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CAT-SCRATCH FEVER

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WITHIN recent years cat-scratch fever (benign inoculation lymphoreticulosis) has come to be recognized as a relatively common disease of man, and the role of the domestic cat in its transmission seems to have been established definitely. While it was first recognized as early as 1930 by Debré,[1] and independently by Foshay in 1932,[2] the disease was not drawn to the attention of American physicians in general until 1951 when Greer and Keefer[3] described the first case recorded in the American literature. Shortly thereafter editorials[2, 4] in both American and British literature urged physicians to be aware of this disease entity which had been known in Europe, particularly in France, for some years. During the past two years more than fifty reports have appeared in the literature recording a total of nearly 200 cases from all parts of the world.

Nomenclature concerning the syndrome requires some clarification: cat-claw disease, cat-scratch disease, cat-bite fever, cat-scratch fever. In American literature cat-scratch fever seems to be the terminology generally accepted. Mollaret and his co-workers[5] have proposed the more descriptive term, benign inoculation lymphoreticulosis, and subsequent authors have agreed upon its applicability. However, the designation, cat-scratch fever, is simple and descriptive, and is likely to remain in common use until the etiology of the disease has been identified more definitely.

The present report is the result of a series of studies carried out in children in the South Texas area. Within the past eighteen months, twelve cases of cat-scratch fever have come to our attention, which emphasizes again the probable widespread incidence and frequent observation of this disease in the everyday practice of medicine. All of these patients showed the characteristic features of the disease.

CLINICAL MANIFESTATIONS

The usual presenting picture in cat-scratch disease is one of malaise, low-grade fever, and unexplained local adenopathy. While, as a rule, the patient does not appear acutely or chronically ill, the size of the involved lymph node, or nodes, is often quite impressive. In most instances the history will reveal some association with cats, although the patient may not remember the location or time of a spe-

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cific scratch. The incubation period is somewhat variable: a survey of cases described in the literature indicated an average interval of from ten to thirty days between the date of probable inoculation and the development of significant regional adenopathy. In the case of one volunteer subject,[5] whose course was followed carefully during the period immediately subsequent to intradermal injection of untreated material from the bubo of a proved case of cat-scratch fever, minimal regional adenopathy began in about eight days. The involved nodes enlarged progressively so that twenty days later a large fluctuant central node was present surrounded by smaller nodes. At the height of the lymph node response, a skin papule appeared at the site of the primary intradermal inoculation, and persisted for several days.

The foregoing sequence observed in a human subject infected experimentally seems to be characteristic likewise of the disease in the patient who is naturally infected. At the time that medical advice is sought by the patient with cat-scratch fever, there is usually an exacerbation of redness and swelling at the site where a primary lesion has been in the process of healing. This lesion tends to heal slowly and may resemble an insect bite, a small pustule or furuncle, a vesicle, or a scab following simple trauma. The involved nodes are limited ordinarily to one anatomical drainage area, e.g., the axillary and epitrochlear, submandibular and cervical, or femoral and inguinal. Inspection may reveal some redness of the skin overlying an enlarged node, but more often the overlying skin is entirely normal in appearance. The individual lymph node may be hard or soft, and varies in size from about 1 × 2 cm. to about 5 × 5 cm. Such a node yields on aspiration a purulent fluid which is sterile when cultured by the usual bacteriologic methods.

Likewise, the usual laboratory studies are nonrevealing, the findings, as a general rule, being within normal limits. However, there may be a moderate leukocytosis with a tendency to a left shift in the differential count. Agglutination tests for *Pasteurella tularensis, Brucella abortus, and Brucella melitensis,* and heterophil antibody test for infectious mononucleosis are negative consistently. While some patients may show a low titer of antibodies[5] to Lygranum antigen by complement fixation test, the intradermal Frei test for lymphogranuloma (Lygranum antigen) is negative. However, patients with cat-scratch fever show uniformly a positive skin reaction when tested by intradermal injection with an antigen prepared by the Frei procedure from the bubo of a known case of cat-scratch fever.[1, 2, 4]

CASE REPORTS

CASE 1.—C. R., a 9-year-old white female (Lovelady, Texas). On Sept. 9, 1952, this child developed a temperature of 104° F. At that time large tender swellings were first noted in the left axilla and on the inner side of the left elbow. One left axillary node and a similar epitrochlear node were red, tender, and enlarged to a size of about 4 × 5 cm. Simultaneously a small healing papule on the back of the left ring finger was noticed which appeared swollen and red, and likewise an erythematous papule about 1 cm. in diameter on the dorsum of the left fourth finger; in all probability the latter represents the primary lesion. The patient had been in association with three cats, one dog and one para-

keet, and while she had been aware at various times of scratches inflicted by all of these pets, she did not remember specific scratches which might have preceded the present lesions. At this time the blood count was essentially normal except that the white blood cells numbered 13,800 with 55 per cent polymorphonuclear cells. Urinalysis gave results within normal limits. Agglutinations for *Br. abortus, Br. melitensis,* and *Past. tularensis* were negative; heterophil antibody test for infectious mononucleosis, and tuberculin skin test gave negative results. The initial therapy consisted of aureomycin, 25 mg. per kilogram of body weight per twenty-four hours. While there was some alleviation of systemic symptoms, there was no appreciable regression of the enlarged nodes, and the temperature remained elevated: 102° to 103° F. each afternoon. After four days, the aureomycin therapy was replaced by penicillin and streptomycin administered twice daily, with no obvious improvement.

On September 29 the patient was admitted to Hermann Hospital, at which time the left axillary and epitrochlear nodes were about 4 × 5 cm. in size, and appeared fluctuant. Laboratory findings at this time were consistent with those reported previously. Chest x-ray revealed no abnormalities. Aspiration of the nodes under local anesthesia yielded purulent material, 5 to 6 c.c. being removed from each node. A portion of this material was cultured by routine bacteriologic methods, on Sabouraud's medium and on special media for the detection of the tubercle bacillus. No growth was obtained by any of these means. The major portion of the aspirated material was subjected to the Frei procedure and was used as a skin-test antigen. Approximately one month after the onset of lymphadenopathy the patient's skin reaction to intradermal injection of 0.1 c.c. of this antigenic material was strongly positive. In the weeks following, there was gradual regression of the enlarged nodes and the patient became afebrile.

CASE 2.—C. C., a 5-year-old white female (Houston, Texas). On June 30, 1952, this patient became febrile, elevation to 102° F., and simultaneously a tender swelling was noted on the inner aspect of the left elbow. Since the child did not complain or appear ill, two days elapsed before the advice of a physician was sought. At this time bacterial adenitis was suspected and the therapy employed was 400,000 units of intramuscular procaine penicillin. The fever subsided in two to three days, but the red, swollen tender mass at the left elbow was enlarging rather than regressing. On July 14 this patient was seen in consultation, and at that time several red, indurated papules were evident on the dorsum of the left hand. Apparently, these papules had appeared about one week following the onset of lymphadenitis, their presence being attributed by the parents to a "scratch that festered." The family is in the habit of keeping household pets and had a cat at the time of the present illness.

Blood studies carried out at the time of consultation showed a white blood cell count of 12,800 with 47 per cent polymorphonuclear cells. The patient was placed on aureomycin therapy, 25 mg. per kilogram of body weight per twenty-four hours, for a period of ten days. During this ten-day period the lesions on the hand regressed, and there was a definite change in the enlarged node from hard to fluctuant. At this time the fluctuant node was incised and drained, yielding about 10 c.c. of purulent material, in which no bacteria could be demonstrated on direct smear and no bacterial growth by the usual culture methods. A draining sinus at the aspiration puncture site persisted for several weeks, clearing very gradually. Approximately four months following the onset of disease, this patient showed a positive skin reaction to intradermal injection of the antigen prepared from the first case of cat-scratch fever.

CASE 3.—C. A., a 16-month-old Latin-American male (Houston,

Texas). This patient was admitted to Jefferson Davis Hospital in November, 1952. At the time of admission, the child was febrile, temperature 103° F., and showed moderate respiratory dyspnea. On examination, the only positive finding was the presence of an enlarged, left inguinal lymph node with some discoloration of the overlying skin. At this time, however, a number of partially healed scratches and papules were noted on the patient's ankles which showed some erythema. According to information obtained from the family, the enlarged node had appeared three to four weeks previously, and had been moderately tender at one time. The child had been in close association with a cat, but a specific instance of scratch or bite could not be elicited. X-ray examination of the chest on admission revealed an area of infiltration in the right upper lobe, compatible with pneumonitis. The patient was followed carefully by daily x-ray examination and this infiltration cleared completely within three days. Admission white blood cell count of 54,700 fell to 9,200 cells within four days following hospitalization. Frei test and tuberculin skin test gave negative results. Repeated agglutination tests for *Br. abortus, Br. melitensis,* and *Past. tularensis* were negative; heterophil antibody test for infectious mononucleosis likewise gave negative result. While antibiotic therapy (penicillin, streptomycin, and terramycin) did not bring about any change in the enlarged left inguinal node, the general condition of the patient improved; the temperature returned to normal, and the leukocytosis and pneumonitis subsided. Three weeks later this patient showed a strongly positive skin reaction to intradermal injection of antigen prepared from the first case of cat-scratch fever.

CASE 4.—J. R., a 5-year-old white female (Houston, Texas, patient seen through the courtesy of Dr. Byron York). On Nov. 27, 1952, the parents noticed swelling and soreness in the right inguinal region. As the child did not appear ill and was afebrile, a physician was not consulted until December 16, by which time the swelling and tenderness had become more apparent. On examination, a right inguinal lymph node was found to be enlarged to a size of about 2 × 3 cm., but no primary lesion could be identified on the right leg. History taken at this time revealed that on numerous occasions during the past year the child had been in close association with cats. No specific therapy was employed and the enlarged node gradually subsided during the next three weeks. Skin test reaction with antigen from Case 1 of this series was strongly positive about six weeks following onset of lymphadenopathy.

CASE 5.—J. B. H., a 5-year-old white male (Houston, Texas). On Oct. 20, 1951, this patient's mother first noticed a "kernel" in the left axilla. While the child did not appear ill, the temperature at this time was 100° F.; during the ensuing five days, the "kernel" increased in size and the area became tender. When this child was first seen by a pediatrician on October 26, two tender left axillary nodes were noted which were about 3 cm. in diameter. Aureomycin therapy was initiated, 30 mg. per kilogram body weight. Within a few days' time the low-grade fever subsided, but the nodes remained hard, enlarged, and tender. Daily administration of 400,000 units of procaine penicillin for four days had no effect on the nodes, nor did six days of chloramphenicol therapy (60 mg. per kilogram of body weight per twenty-four hours) bring about any change. The involved nodes gradually became fluctuant, and subsided without spontaneous suppuration within about five weeks after the patient was first seen. Laboratory studies during the acute phase revealed a white blood cell count of 12,000 with 65 per cent polymorphonuclear cells, negative tuberculin test, negative agglutination tests for *Br. abortus* and *Br. melitensis,* and negative heterophil antibody test for infectious mononu-

cleosis. The family had acquired a cat in August, 1951, two months prior to the onset of illness in the child, but no specific instance of scratch could be elicited. The cat died in November, 1951, the cause of death being given as pneumonia. In November, 1952, one year after the onset of illness, a skin test was performed on this patient using antigen from the case described here as Case 1. A strongly positive reaction resulted from intradermal injection of this antigen.

CASE 6.—P. C., a 4-year-old white male (Houston, Texas). This patient was first seen on July 24, 1952, because of a tender swelling in the left axilla, being brought in by his nurse since his mother had been hospitalized for a surgical procedure. While the child had been in close contact with cats intermittently at the home of his grandparents, the nurse was not aware of any specific primary lesion. Physical examination revealed nothing of note except four to six palpable left axillary nodes, one of which was about 4 cm. in diameter. As the patient was afebrile, and had no complaints, he was not returned for observation. The enlarged nodes were reported to be regressing slowly.

Four months later (November, 1952) this boy was seen because of another illness, and at this examination there were still several small palpable nodes in the left axilla, the largest being about 2 cm. in diameter. Tuberculin skin test at this time was negative; blood cell count and urinalysis were within normal limits. This re-examination after four months afforded an opportunity for a skin test with the cat-scratch antigen from Case 1. This reaction was strongly positive.

CASE 7.—J. L. K., a 5-year-old white male (Conroe, Texas). In January, 1952, this patient developed fever (104° F.), headache, and pain above the left elbow. Physical examination was nonrevealing except for a tender, left epitrochlear node about 1.5 cm. in diameter, and a tender, left axillary node, 3 cm. in diameter. He was placed on a daily regimen of 400,000 units of procaine penicillin administered intramuscularly for five days. During this therapy the temperature elevation subsided. Agglutination tests for *E. typhosa, Br. abortus, Br. melitensis* gave negative results. Likewise heterophil antibody test for infectious mononucleosis was negative. For some months prior to the onset of illness this child had been in frequent close association with cats. The subsequent course of the enlarged nodes is not known, but the patient was seen ten months later, in November, 1952, and a nontender, firm node about 2 cm. in diameter was still present in the left axilla. At this time an intradermal skin test performed with cat-scratch antigen was positive.

CASE 8.—R. W., a 5-year-old white male (Houston, Texas). This patient first began to complain of pain and tenderness in the left groin on Oct. 8, 1951. However, a physician was not consulted until October 15, at which time examination revealed three enlarged nodes which were markedly tender, left inguinal 1 cm. in diameter, left iliac about 4.5 cm. in diameter, and left femoral about 1 cm. in diameter. Tuberculin skin test performed at this time was negative, as was a heterophil antibody test for infectious mononucleosis. Agglutination tests for *Br. abortus* and *Past. tularensis* likewise were negative. Roentgenographic examination of the chest showed no abnormalities. Therapy consisted initially of penicillin and chloramphenicol in combination and later of aureomycin alone, 30 mg. per kilogram of body weight per twenty-four hours with no obvious regression of the enlarged nodes. Within the following three to four weeks, all three of the enlarged nodes gradually diminished in size, but two and one-half months after onset of illness, the left iliac node was still about 3 cm. in diameter. While no definite history of contact with cats could be obtained, this patient did have white mice as pets. In December, 1952, an opportunity for re-examination of

this child was afforded; the left iliac node was no longer palpable, and at this time a skin test with cat-scratch antigen was performed. The result was strongly positive.

CASE 9.—F. J., a 10-year-old white male (Houston, Texas, patient seen through courtesy of Dr. A. Aaron Mintz). On Jan. 6, 1953, this patient appeared at the Jefferson Davis Hospital complaining of malaise and pain associated with a large fluctuant mass in the right axilla. History revealed that the boy was in close contact with both a cat and a dog. He remembered no specific instances of cat scratches, but displayed several scars on both hands which were thought to have been inflicted by the dog. Approximately six weeks previously he had noticed a small tender area in the left axilla. This lesion increased in size and the overlying skin became discolored. There had been no apparent systemic disease and no fever associated with this first episode.

On examination a fluctuant lymph node was noted in the right axilla about 4 × 8 cm. in size, and immediately above this, a nontender node about 1 cm. in diameter which was not fluctuant. There was a purple discoloration of the overlying skin. The skin on the dorsum of the right hand showed several blemishes, one a scab, and one composed of two linear papules. Tuberculin test was negative; white blood cell count was reported as 4,400 with 55 per cent polymorphonuclear cells. The patient was admitted to the hospital; the fluctuant node was incised and drained, yielding 35 to 50 c.c. of purulent material which gave no growth when cultured by routine bacteriologic methods. The resulting cavity was packed with approximately 18 inches of iodoform gauze, which was removed within forty-eight hours, with subsequent rapid clearing of the disease process. There was gradual regression of the smaller nonfluctuant node. Several days after admission a skin test for cat-scratch fever was positive.

CASE 10.—E. J., a white female, aged 2 years 6 months (Houston, Texas, patient reported through the courtesy of Dr. R. D. Lomas). On Sept. 18, 1952, this patient developed an upper respiratory infection with low-grade fever and cough. When these manifestations began to subside within five to six days, the mother first noticed a swelling in the left axilla. She was first seen by her physician on September 24, at which time a moderately enlarged, left axillary node was present. Since antibiotic (penicillin, chloramphenicol) and sulfonamide therapy failed to alter the condition, the child was hospitalized for study.

Examination on admission revealed an essentially healthy child who did not appear ill or uncomfortable. A mass was noted in the left axilla about 4 × 4 cm. which was moderately tender with overlying skin erythematous. A papule was observed on the left thumb which had appeared about one week previously, attributed by the parents to an insect bite. They did report, however, that this area of the child's hand had been licked by a stray cat several weeks previously. On admission the white blood cell count was 18,000 with 85 per cent polymorphonuclear cells; subsequently this count fell to 11,500 with 75 per cent polymorphonuclear cells. Agglutination studies at the time of hospitalization and when repeated three weeks later gave negative results: heterophil, typhoid, paratyphoid A and B, typhus, brucellosis. Other studies included bone marrow examination, blood culture, sedimentation rate and urinalysis, all showing results within normal limits. Tuberculin tests (PPD, first and second) were negative, and chest x-ray was nonrevealing. A skin test performed with cat-scratch antigen from Case 1 was strongly positive. On aspiration the involved node yielded 15 c.c. of bacteria-free exudate. An antigen was prepared from this material which likewise gave strongly positive reaction on intradermal injection. For control purposes, this antigenic material was tested intradermally in the patient's

mother and in a patient with infectious mononucleosis, both tests giving negative results. The patient's symptoms subsided and the enlarged nodes receded gradually.

CASE 11.—C. McF., a 10-year-old white female (Houston, Texas, patient seen through the courtesy of Dr. S. G. Ohlhausen). This patient was seen by a physician on Jan. 11, 1953, because of bilateral inguinal lymphadenopathy, the nodes having been enlarged and tender in both inguinal areas for a period of about two weeks. Approximately four weeks prior to the onset of the present illness the patient had acquired a stray cat. At the time of examination by a physician numerous scratches were visible over both lower extremities and the mother stated that this pet had scratched the girl's legs so frequently that she had been forced "to give the cat away." The physician recommended hospitalization for purposes of diagnosis and treatment. On admission, the patient was afebrile and in no particular discomfort. At this time the lymph node in the right inguinal region was about 3 × 4 cm. in size, the node in the left about 2 × 3 cm. in size. Both nodes were tender and the overlying skin was discolored. Examination of the lower extremities revealed multiple linear abrasions and on the right leg a recent eschar 1 cm. in diameter.

Laboratory findings were nonrevealing; urine and blood studies gave results within normal limits; agglutination tests for brucellosis and tularemia were negative as were the tuberculin test and the Frei test. Chest film was described as normal. Intradermal skin test performed with cat-scratch antigen from Case 1 gave strongly positive reaction, the erythema and induration at the site of injection being easily visible five days after the test had been performed.

Aspiration of involved nodes was carried out on the twelfth hospital day, about 5 c.c. of bacteria-free purulent material being obtained from each.

CASE 12.—J. C. S., a white female, aged 2 years 3 months (Velasco, Texas). This patient was seen in consultation on March 4, 1953, because of an enlarged right axillary lymph node. History revealed that on February 5 of this year the patient had developed a temperature of 104° F. On the day following, the parents noted a tender swelling in the right axilla. A small "pimple that seemed to fester about this time" was noted on the right middle finger. The child was attended by a physician who prescribed sulfonamides. Two days later, since the fever was still high, and the enlarged nodes showed no improvement, therapy was changed to aureomycin, 100 mg. every four hours (total daily dose, 50 mg. per kilogram of body weight) for seven and one-half days. On this regime the fever subsided, the node seemed less tender, but had not diminished in size.

Examination on March 4 showed nothing of consequence except the presence of an enlarged node (about 3 × 4 cm.) in the right axilla, with a central overlying area of erythema, and an erythematous papule, 3 × 4 mm. in size, on the dorsal aspect of the right middle finger. The patient had acquired a cat six months prior to the onset of the present illness, and a dog one month later. Both animals were apparently well throughout this period. On various occasions both animals had scratched the child about her hands and legs.

Skin tests were performed on this patient employing antigens prepared from Cases 1 and 11; both gave similar strongly positive reactions. As long as five days after these intradermal antigenic tests, the skin response was clearly evident.

The involved node was aspirated yielding 2 to 4 c.c. of gray purulent material which gave no growth on the usual bacteriologic media. By March 16, six weeks after onset, the skin lesion on the finger had cleared and the axillary node was reduced in size to about 1 × 2 cm.

DISCUSSION

Two findings appear common to all the cases reported here (Table I): the presence of one or more lymph nodes enlarged significantly, and the occurrence of a clearly positive reaction to intradermally injected antigen which was prepared from the bubo of the patient in Case 1. Skin reactions were found to be positive from one to fourteen months after the onset of lymphadenitis. In two of the cases both axillary and epitrochlear glands on one side were involved, whereas in six, epitrochlear or axillary involvement alone occurred. In four instances involvement was limited to the inguinal region. A typical primary lesion was identified definitely in only seven cases. In three of the earlier cases a careful search for the primary site had not been made at the time when it might have been evident. In the remaining two cases no definite primary site could be identified, although blemishes of the distal skin were noted.

TABLE I. CLINICAL SIGNS, SYMPTOMS, AND RESPONSE IN TWELVE CASES OF CAT-SCRATCH FEVER

	NO. CASES
Tender, enlarged lymph nodes	12
Positive skin test	12
Known cat contact	10
Primary lesion	
Definite	7
Indefinite	3
Absent	2
Fever	9
Leukocytosis	8
Pus obtained by aspiration, sterile	7
Malaise	4
Response to Therapy of Eight Patients Treated With Antibiotics	
Fever subsided	8
Node regressed	0
No specific therapy	4

Temperature elevation, present in all except three cases, ranged from 100° to 104° F., and was often characterized by daily spikes for a period of several weeks. With the exception of moderate leukocytosis, laboratory findings were consistently nonrevealing. In one instance, the patient had a marked leukocytic response associated with a transient pulmonary infiltration. While none of the lymph nodes showed spontaneous suppuration, in each of seven instances where aspiration was performed, the node contained an abundance of purulent material, reported as sterile by ordinary bacteriologic culture methods. With the exception of one patient, who had acquired several white mice as pets shortly before the onset of illness, all of the patients admitted frequent association with cats. While response to antibiotic therapy was not dramatic in any of the patients observed, aureomycin did seem to ameliorate systemic symptoms in some degree.

Skin Testing: Preparation of Antigen.—The following procedure constitutes a convenient method for preparing skin-test antigen from a known case of cat-scratch fever, and can be carried out on the hospital ward. Aspiration of a suppurative node is performed under strictly aseptic conditions. The purulent material obtained is injected directly into a sterile puncture-type vial containing 2 to 3 c.c. of normal saline and the vial shaken vigorously in order to insure thorough dispersion. Additional saline solution is injected into the vial immediately, enough to result in an approximate 1:5 dilution of the exudate. In our experience no anticoagulant is necessary if dilution of the purulent material is accomplished without delay. On each of two successive days the diluted material is heated for one hour, at a

temperature of 56° to 60° C. If this potentially antigenic material is shown by bacteriologic culture to be sterile, it is tested intradermally in volunteers in order to rule out nonspecific skin reactions.

The skin test is performed as in a tuberculin test by the intradermal injection of 0.1 c.c. of the antigen, the site being observed at intervals of forty-eight and seventy-two hours after the injection. Positive reaction con-

TABLE II. SUBJECTS SHOWING NEGATIVE SKIN REACTION TO THE ANTIGENS PREPARED FROM CASES OF CAT-SCRATCH FEVER (CASES 1, 10, AND 11)

"CONTROL" PATIENT	AGE	SEX	ANTIGEN USED PREPARED FROM	CLINICAL STATUS
1.	2 mo.	M	Case 1	Hydrocephalus and spina bifida
2.	4 mo.	F	Case 1	Multiple congenital malformations
3.	35 yr.	F	Case 1	Nonsick mother of Patient 1
4.	9 yr.	M	Case 1	Spinal cord tumor; convalescent
5.	2 yr.	F	Case 1	Cervical adenitis; responded to penicillin therapy
6.	4 yr.	M	Cases 1 and 11	Suppurative axillary adenitis; responded to incision and drainage
7.	5 yr.	M	Cases 1 and 11	Suppurative axillary folliculitis with spontaneous drainage
8.	6 yr.	M	Case 1	Suppurative inguinal adenitis secondary to impetigo on leg; good response to antibiotics
9.	9 yr.	M	Case 1	Lymphosarcoma, generalized
10.	7 yr.	M	Case 1	Lymphadenopathy secondary to primary smallpox vaccination
11.	4 yr.	M	Cases 1 and 11	Cervical adenitis readily responsive to antibiotics
12.	7 yr.	M	Cases 1 and 10	Infectious mononucleosis
13.	31 yr.	F	Cases 1 and 10	Nonsick mother of Patient 10
14.	12 mo.	F	Cases 1 and 11	Suppurative axillary adenitis associated with primary vaccination
15.	15 yr.	F	Cases 1 and 11	Cervical adenitis—chronic, nonsuppurative
16.	3 yr.	F	Case 11	Submandibular tuberculous adenitis (scrofula)
17.	9 yr.	M	Case 11	Suppurative inguinal adenitis
18.	5 yr.	M	Cases 1 and 11	Suppurative axillary adenitis
19.	5½ yr.	F	Cases 1 and 11	Supraclavicular adenitis
20.	5 yr.	F	Case 1	Infectious mononucleosis
21.	4 yr.	F	Case 11	Suppurative parotitis

sists in an indurated, raised, erythematous wheal from 5 to 10 mm. in diameter which is surrounded by a zone of erythema from 30 to 40 mm. in diameter. This reaction may disappear in one to two days, but, as a rule, the wheal can be recognized readily as long as four to five days later. In a negative response there is no associated erythema, induration, or swelling of the injected tissue. No regional adenopathy occurs in response to intradermal injection of the antigen either in patients with cat-scratch fever in whom the reaction is positive, or in subjects in whom the reaction is negative.

In the present series skin tests were carried out using the antigen prepared from Case 1. All patients in whom a diagnosis of cat-scratch fever could be made on the basis of clinical manifestations showed positive skin reaction to this antigen. By way of comparison, a group of "control" subjects was tested with this antigen, this group consisting of normal volunteers, of patients with no evidence of lymph node disease, as well as of patients with suppurative or nonsuppurative adenopathy thought to be attributable to other causes than cat-scratch fever. Complete absence of response in normal volunteers seemed to rule out the possibility of nonspecific skin reactions to the antigen. The results of these intradermal tests carried out for purposes of comparison were negative consistently (Table II). No untoward effects of any kind occurred as a result of the injection of the antigenic skin-testing materials.

Subsequently, skin-test antigens were prepared from material obtained by needle aspiration of the involved nodes in two additional patients (Cases 10 and 11). These antigens were used for the skin testing of known positive and known negative subjects. In nine of the control patients, as indicated in Table II, two of the three antigens prepared were injected simultaneously at two different sites. All three antigen samples gave similar results: positive skin reactions in patients with cat-scratch fever and negative reactions in controls, irrespective of the sample of antigen employed.

Variation in Clinical Manifestations.—While the majority of the patients reported has shown clinical manifestations similar to those observed here, interesting variations have been described by a number of authors. Two cases have been reported[2, 6] in which there was apparent inhalation or aspiration of the etiological agent into the throat, with subsequent cervical adenitis. Lange[7] noted a cough and transient pulmonary infiltration in one of his patients who showed characteristic manifestations of cat-scratch fever and who gave a definite history of scratches. An oculoglandular form of the disease is described in the French literature[8] which was associated with conjunctivitis and adenopathy of the cervical nodes. Greer and Keefer[3] report a patient with cat-scratch fever in whom the clinical picture was dominated by an erythema-nodosum-like exanthem. Recently Stevens[9] has described a 13-year-old boy in whom there was a severe but transient encephalitis, associated with an identifiable primary lesion on the right forearm, enlargement of axillary and epitrochlear lymph nodes on the right side and a history of cat scratch. The illness was characterized by high fever, generalized convulsions, and coma for a period of forty-eight hours. Diag-

nosis of cat-scratch fever was made in retrospect two and one-half years later when a typical positive skin reaction to specific antigen was obtained. Stevens suggests that this patient may represent a case of cat-scratch encephalitis.

Differential Diagnosis.—The cat-scratch syndrome is most commonly confused with simple pyogenic adenitis, but may be differentiated by the isolation in the latter of a causative bacterial agent, and by clinical response to antibiotic therapy. In the presence of a positive tuberculin test, tuberculous adenitis must be considered. The early cases observed by Foshay[2] were encountered during an outbreak of tularemia. Foshay recognized that, while the clinical picture bore many resemblances to tularemia, such patients were less ill, failed to show positive skin tests to tularemia antigen, and did not develop agglutinating antibodies for *Past. tularensis.* At that time Foshay suspected cat scratch as a means of transmission in this disease, but unfortunately made no report of his findings in the medical literature. In atypical cases, Hodgkin's disease and malignant lymphoma must be considered in differential diagnosis. Patients with inguinal involvement have been described in whom the diagnosis of lymphogranuloma venereum was considered until the possibility of cat-scratch fever could be investigated. Fungus infection such as sporotrichosis can be differentiated, as a rule, by characteristic clinical features and by appropriate laboratory studies.

Treatment.—No specific therapeutic measures have been of definite benefit in cases proved by skin test reaction. Aureomycin seems to shorten the febrile course in some instances. Lange[7] noted that the nodes regressed more rapidly during chloramphenicol and/or terramycin therapy. Occasionally, aspiration drainage will hasten the resolution of fluctuant nodes, although the procedure may result in the development of a draining sinus. Such draining sinuses invariably heal, leaving only a minor scar.

Prognosis.—The prognosis in cat-scratch fever is uniformly good. The enlarged nodes show spontaneous regression in one to three months after reaching their peak enlargement. In some instances fibrosis may result in persistence of the nodes indefinitely. With few exceptions, systemic signs and symptoms are mild and self-limited.

Pathologic Findings.—Lymph node biopsy material and lymph nodes excised in toto from patients showing typical clinical manifestations of cat-scratch fever have been studied in detail.[2, 5, 10] Consistently nonspecific morphologic changes have been described. Mollaret[5] grouped these nodes into three distinct phase classifications: the "elementary" phase of simple hyperplasia of all node elements, the "accentuated" stage in which, in addition to hyperplasia, areas of early cellular necrosis appear which stain as acidophilic masses, and the "ultimate" stage in which the normal orderly lymph node architecture is displaced by multiple areas of central necrosis, and which is characterized by the appearance of circumscribed foci of epithelioid cells and scattered giant cells of the Langhans type. Fox[10] refers to these foci as pseudotubercules. This final phase corresponds clinically to the stage at which the enlarged node

becomes fluctuant and is followed either by slow regression or spontaneous suppuration and healing.

Etiology and Epidemiology.—While the etiology of this disease entity has not been clarified completely, there is considerable evidence indicating that the infectious agent concerned belongs to the psittacosis-lymphogranuloma group of viruses.[11] Transfer of the disease to monkeys and to human volunteers has been accomplished. Bacteriologic cultures and culture on Sabouraud's medium of material aspirated from suppurative lymph nodes have yielded consistently negative results. On microscopic examination, stained sections of primary skin lesions and involved lymph nodes in both man and monkeys show large numbers of intracellular and extracellular granules identical in appearance with the elementary bodies characteristic of psittacosis.[11] These bodies are numerous in early lymph node lesions, especially in the reticulocytes bordering on a zone of necrosis, but may be seen also in more advanced lesions and in lymphocytes, as well as reticulocytes. Although the Frei test is negative consistently, patients convalescent from cat-scratch disease do show by complement fixation low titers of antibody to Lygranum.

Since, as a general rule, cats do not show any apparent morbidity associated with their ability to transmit the disease to human subjects, the role of the cat has been considered a passive one. In those instances in which the involved animal was subjected to skin testing there was no evidence of reaction to the intradermal antigen.[2] In the case of some patients the possibility of cat contact seems to have been excluded, yet in a single family several cases of cat-scratch fever occurred which centered about the family cat. Other means of transfer have been accepted by some authors[1, 5]: scratch by thorn, by wood splinter, by fragments of bone in a meat handler. Mollaret and his associates suggest that the virus may be widespread in animal, and possibly in vegetable life.

Most of the earlier cases were reported from France. It is probable, however, that distribution is actually world-wide since cases have been reported from Great Britain, United States, India, and Switzerland, as well as from France. Daniels and MacMurray,[2] in Washington, D. C., undertook the skin testing of their patients with cat-scratch fever not only with antigen prepared from patients in Washington, but also with antigen prepared from patients in Cincinnati and in Paris, France. Reactions were consistently positive regardless of the particular sample of antigen used, suggesting a basic antigenic similarity in all the cases, a finding which is in accord with observations in the present series in which antigens were prepared from three different patients.

A possible relationship between the etiological agent of cat-scratch fever and that of feline pneumonitis has been suggested.[12] The virus of this feline disease described by Baker gives rise to elementary bodies similar to those associated with psittacosis, and was shown to be related antigenically to viruses of the psittacosis-lymphogranuloma group. Viruses belonging to this group have been identified in connection with infections in other animals associated with man, such as enzootic abortion in ewes[14] (EAE virus), an intestinal infection in calves

which often occurs without obvious clinical manifestations,[15] and pneumonia in sheep.[16]

SUMMARY

This report, concerned with cases of cat-scratch fever, is the result of a series of studies carried out in children in the South Texas area. Within the past eighteen months twelve cases of cat-scratch fever have come to our attention, which emphasizes again the probable widespread incidence and frequent observation of this disease in the everyday practice of medicine. All of these patients showed the characteristic features of the disease: malaise, fever, and unexplained local adenopathy, in which the size of the enlarged lymph node may be quite impressive. The incubation period is somewhat variable, averaging from ten to thirty days. As a rule, the patient does not appear acutely or chronically ill. In most instances the history will reveal some association with cats, although the location or time of a specific scratch may be uncertain. At the time that medical advice is sought, lymphadenopathy is the chief presenting symptom, and there may be an exacerbation of redness and swelling at the site where a primary lesion has been in the process of healing.

Patients with cat-scratch fever show uniformly a positive skin reaction when tested by intradermal injection with an antigen prepared by the Frei procedure from the bubo of a known case of cat-scratch fever. The preparation of this antigen for skin testing is described in detail.

As a basis for comparison in the present study, a group of "control" subjects was tested for skin reaction of the type observed in cat-scratch fever. This group consisted of normal volunteers who showed complete absence of response to intradermal injection of the antigenic material, patients with no evidence of lymph node disease and patients with suppurative or nonsuppurative adenopathy thought to be attributable to other causes than cat-scratch fever. The results of these skin tests were negative consistently. No untoward effects of any kind occurred as a result of the injection of the antigenic skin-testing materials.

In the course of the study, skin-testing antigens were prepared from material obtained by needle aspiration of involved lymph nodes in three separate patients whose signs and symptoms were typical of cat-scratch fever. All three antigen samples gave similar results.

With few exceptions the disease is mild and self-limited. No specific therapeutic measures have been of definite benefit in cases proved by skin-test reaction. Aureomycin seems to shorten the febrile course in some instances and to alleviate the systemic symptoms in some degree.

While the etiology of this disease entity has not been clarified completely, there is considerable evidence in support of the view that the infectious agent concerned belongs to the psittacosis-lymphogranuloma group of viruses.

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SERUM CORTICOIDS IN CHILDREN UNDER STRESS

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RESPONSE to stress is marked, both in adults and in children, by an increased urinary excretion of 17-hydroxycorticosteroids. Nelson and associates,[1] however, found no rise in the blood level of 17-hydroxycorticoids in adults with serious infections except just before death when these patients showed an increased blood concentration. Nelson also showed that ACTH administration will produce a dramatic rise in blood corticoid levels. This has been verified in children by Raile and co-workers.[2] Tyler and associates[3] have reported that the blood 17-hydroxycorticoids level rises several hours after operation in normal adults, but that the blood concentration returns to normal within twenty-four hours. The present study shows that responses in children differ from those in adults.

MATERIALS AND METHODS

Blood 17-hydroxycorticoids were measured by the method of Nelson and Samuels,[4] using Florisil as the chromatographic agent.† The only modification in the method was that serum was used in most instances instead of plasma.

There were forty-one individuals comprising the control group. The subjects were laboratory workers in good health and children who were in apparent health but were in the hospital for investigation of behavior problems, neurological disturbances, or who had recovered entirely from minor respiratory illnesses. Sera were also obtained from seventeen patients with acute meningitis. These sera were obtained on the day of admission to the hospital as were the sera from another group of seven patients who had pneumonia or acute tonsillitis and pharyngitis with temperatures above 103° F. Sera were obtained from seven patients with less severe respiratory illnesses. Finally sera were obtained after surgery from nineteen patients; pre- and postoperative specimens were drawn from seven of these children.

RESULTS

The mean free serum corticoid level in the forty-one normal children and adults was 13.0 μg per 100 ml. with a standard error of the mean of ± 1.21. This agrees with the mean reported by Kelley and Ely[5] for children and by Nelson for adults. The mean level of free 17-hydroxycorticoids in the sera of sixteen children with acute meningitis was 88.5 μg per 100 ml. with a standard error of the mean of ± 9.6. No correlation could be found between the level of blood corticoid and the age of the patient with meningitis or the specific infecting organism. The ages of the patients with meningitis ranged from 3 months to 8 years.

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†Standard compound F was kindly supplied by Dr. W. G. Haines, The Upjohn Company.

There were three patients with meningococcal meningitis, three with streptococcal meningitis, three and questionably four with pneumococcal meningitis, and five with *H. influenzae* meningitis. There was also one child who had tuberculous meningitis. All these patients recovered uneventfully. In addition, there was one 2-year-old girl who entered the hospital with a history of fever of six hours' duration. Physical examination revealed a stiff neck but the child was communicative, cooperative, and ate well. Examination of the cerebrospinal fluid proved the diagnosis of meningococcal meningitis. On entry her serum corticoid level was 13.0 μg per 100 ml. Eighteen hours later it was 58.0 μg per 100 ml. The mean corticoid level of four of these patients was down to 24.8 μg in twenty-four to forty-eight hours.

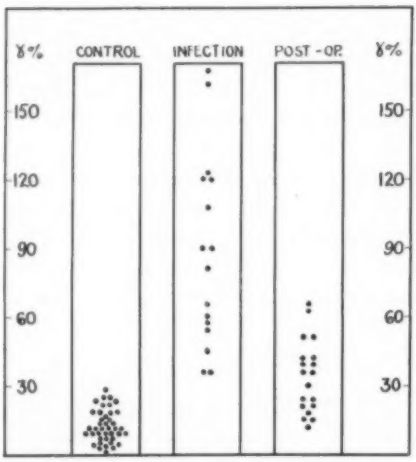

Fig. 1.—Free corticoids in sera of normal children and adults, children with acute meningitis, and in children twenty-four hours following surgery.

The mean level in seven children acutely ill with pneumonia or pharyngitis and tonsillitis was 72.0 with a range of 54.0 to 106.0. These children with acute upper and lower respiratory infections all had temperatures of at least 103° F. Children with less severe respiratory infections had free serum corticoids in the upper end of the normal range with a mean of 20.7.

The mean level of free serum corticoids twenty-four hours after operation in nineteen children was 33.8 μg per 100 ml. with a standard error of the mean of ± 3.5. The average rise in serum corticoids in the seven patients with preoperative as well as twenty-four-hour postoperative blood level determinations was 230 per cent. These children included four whose level twenty-four hours after operation was not beyond the normal range. Fig. 1 graphically compares the levels obtained from normal adults and children, children with meningitis, and children after surgery.

DISCUSSION

Children after stress have higher serum levels of 17-hydroxycorticoids than do adults but this does not necessarily imply that their adrenals are more responsive to stress. The alternative explanation that children have a slower removal of corticoids from the blood is more attractive.

Nelson and associates[1] have suggested that a lowering of utilization (degradation to 17-ketosteroids by the liver should probably be included in this term) causes the preterminal rise in blood 17-hydroxycorticoid levels seen in adults.

In addition to this factor in rate of removal of blood corticoids, the rates of conjugation by the liver and excretion by the kidneys must be considered. The same possibilities exist to explain

the high levels that children continue to show twenty-four hours after surgery. Tyler and collaborators[3] have shown that blood 17-hydroxycorticoid levels return to normal twenty-four hours after surgery in adults and we have verified this in a small number of adult patients. It is our feeling that the second group of factors rather than differences in rate of secretion of these hormones by the adrenals accounts for the differences between blood levels in children and adults undergoing stress. There is also a possibility that the adults tested by Nelson and co-workers,[1] were not undergoing the same degree of stress as the children measured in this study. However, the results following surgery should be comparable and would indicate that the discrepancies in the results are not due to differing degrees of stress.

The differences between the normal serum levels and the levels in patients with meningitis and after surgery are obviously significant. ($t = 8.0$ and 5.6, respectively. $P < .01$ in each case.) Technically the differences between the normals and the two groups with respiratory infections are also significant ($P < .01$ in each case) but the numbers are really too small for this sort of analysis.

SUMMARY

The level of free serum 17-hydroxycorticoids rises dramatically in children with serious infections in contradistinction to previous reports of levels in adults with infection. In addition, the levels tend to remain elevated for a longer period in children than they do in adults following surgery. This may not be due to a difference in adrenal response, but more likely is caused by differences in excretion and degradation or conjugation of the hormonal products.

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AN UNUSUAL FORM OF CENTRAL NERVOUS SYSTEM DISEASE IN A NEWBORN INFANT

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THIS case of demyelinating encephalopathy dating from the first week of life is reported for the purpose of stressing the difficulties incurred in diagnosis, management, and supportive therapy. No attempt will be made to review the varied clinical descriptions appearing under this diagnosis, although a brief perusal of the literature in English failed to disclose a case with as early an onset as the one reported here. Of specific interest is the apparent lack of familial characteristics or consanguinity in this case.

CASE REPORT

A 6-week-old white female was hospitalized for observation of suspected central nervous system disease. She was the product of a full-term, uncomplicated pregnancy of a 22-year-old Rh-negative white primipara. The duration of labor was four hours with delivery accomplished under saddle anesthesia and low forceps. The baby appeared normal at birth, weighing 7 pounds 13 ounces. She left the hospital on the fifth hospital day, without apparent abnormalities.

Shortly after arriving home, the mother observed the baby to be generally tense and rigid. The infant tended to hyperextend the neck, and cried almost constantly while awake.

At 4 weeks of age, slight convulsive movements were observed in both arms, occurring two or three times a day. Following the feedings, which often required one and one-half hours, twitching of the arms and legs was noted. Shortly thereafter when the infant was seen for the initial monthly examination, the mother complained her baby never seemed to relax, except intermittently during sleep. Physical examination was considered normal at this visit.

By 6 weeks of age, the twitchings had become generalized convulsive jerkings varying in duration from five minutes to three hours, frequently beginning in the waist and progressing to the arms, legs, and head. The activity and duration of the convulsions were of such intensity as to preclude proper feedings; regurgitation followed on some occasions, with frank vomiting two days prior to admission. There was no history of cyanosis or respiratory difficulty.

Physical examination on admission revealed the following: Weight 9 pounds 12 ounces; temperature 99.6° F. rectally; pulse 140; blood pressure 90/60. The infant appeared well developed and well nourished. She convulsed continuously with the arms and legs "jerking" at five- to ten-second intervals; concomitantly the head would suddenly hyperextend. At this time there was no involvement of the facial or abdominal muscles. The anterior fontanel measured 2 cm. in diameter and was not tense or bulging. The pupils were round and regular with sluggish reactions, but without nystagmus. Funduscopic examination was not entirely satisfactory; however, it was felt that no gross pathological process was present. Auscultation of the heart and lungs was normal. A very prominent Magnus-deKleijn neck reflex could be elicited. Reflexes in

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the upper extremities were normal, in the lower, absent.

On admission, penicillin, streptomycin, and Chloromycetin were initiated in conventional dosage as were intravenous fluids. Phenobarbital was used to attempt control of the convulsions. Within two hours after admission, the temperature rose to 103.8° F., the convulsive activity had become more rapid with increased irritability. Institution of antipyretic measures dropped the temperature to subnormal where it remained despite measures to raise it. Initial lumbar punctures were unsuccessful; the following morning a successful lumbar puncture was accomplished, showing many nonerenated red blood cells. Laboratory results are shown in Table I.

there were only slight fibrillary twitchings; however, her general condition remained unimproved.

Roentgenograms of the heart, lungs, cervical spine, and skull were of no positive value.

The electroencephalogram was reported as "Basic pattern is not discernible due to much movement artefact while awake. While awake, patient had numerous short grand mal seizures which showed on the EEG record as paroxysmal burst of multiple large amplitude spikes occurring simultaneously in all cortical areas. Diagnostic impression: Abnormal awake EEG with grand mal seizures, discharges occurring simultaneously in all cortical areas. Normal sleep EEG." Fig. 1 shows a portion of the electroencephalogram.

TABLE I. SUMMARY OF LABORATORY RESULTS

DATE	RBC	Hgb	WBC	L	P	URINE	SPINAL FLUID
May 28 (admission)	4.3 mil.	13 Gm. 83%	16,350	51	47	3-5 WBC/LPF	
May 29			15,350	36	61		
June 1 (lumbar tap)							1 lymphocyte 84 mg. % sugar 1,000 mg. % protein 700 mg. % chlorides
June 2						OCC RBC 8-10 WBC/LPF	
June 5		85%	6,700	80	20		
June 9 (ventricular tap)							50 RBC No WBC 125 mg. % sugar 250 mg. % protein 650 mg. % chlorides

Throat culture (May 28), Hemolytic *Staph. aureus*, coagulase-positive.
Blood culture (May 28), *Micrococcus tetragenes.*
Spinal fluid culture (May 28) (reported 8 days later), *Micrococcus tetragenes.*

Bilateral subdural taps were negative on the third day. At that time the initial spinal fluid yielded a growth of gram-negative diplococcus and *Micrococcus tetragenes.* Blood culture obtained on admission was reported growing *M. tetragenes.* Throughout this period, the twitching activity continued with a transient episode of cyanosis on the fourth day following a feeding. A repeat lumbar puncture was performed on that day and a pellicle formed within ten minutes. By the fifth hospital day

The neurosurgical consultant, on the ninth hospital day, advised ventricular taps which were accomplished without incident, and methylene blue was injected into the right ventricle. Several hours later, immediately prior to lumbar puncture, she cried out loudly, marked hyperextension of the neck occurred, followed by extreme pallor and flaccidity. Laryngeal spasm and inspiratory stridor developed, as did transient intense cyanosis. A small amount of frothy sputum was aspirated from the pharynx and in-

creasing quantities of "chocolate-colored" mucus were aspirated from the posterior pharynx. Intravenous calcium gluconate and subcutaneous epinephrine were administered without noticeable effect. The baby progressively worsened with respirations becoming increasingly labored. Early on the tenth hospital day she expired.

Microscopically, the lung showed a collapse of many of the alveoli on one of the sections, and a less noticeable loss of the air sacs on the other sections. All capillaries were dilated, and packed with red cells. Many of the alveoli were filled with a homogeneous

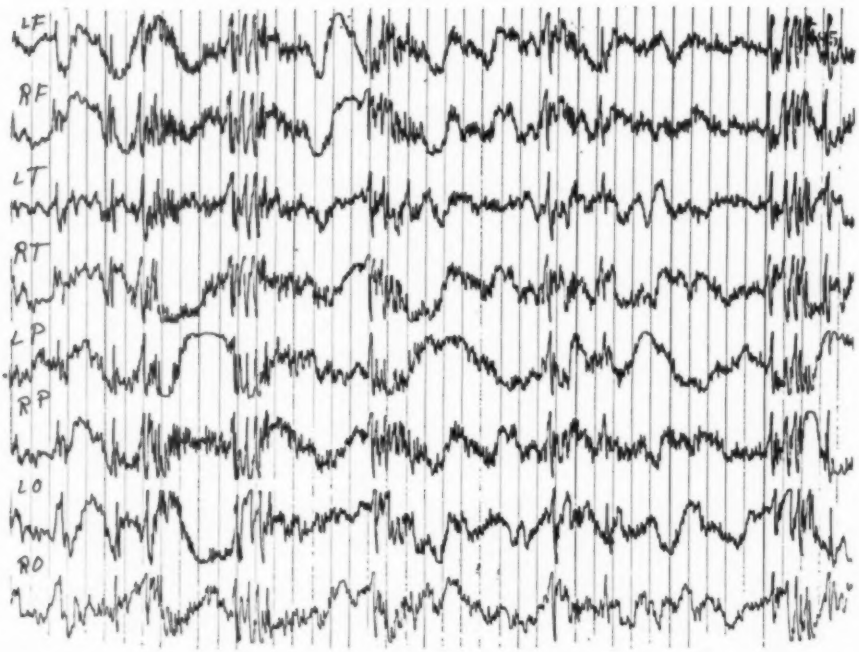

Fig. 1.—Electroencephalogram while patient was awake and having clinically observed grand mal seizure. Tracing during sleep was normal. Amplitude measured in milliamps, standardized to 50 ma. Time interval 1/5 second between lines.

An autopsy was performed. The positive pathological findings were limited to lungs and the central nervous system.

Lungs: The right lung weighed 48 grams, the left lung 38 grams. They were of the expected size. Consistency was that of rubber, and there appeared to be no air in the lungs. The pleura was smooth and glistening. The bronchi were not obstructed or dilated, and there were no enlarged hilar lymph nodes. The cut surface of each lobe was a homogeneous pale pink color pink-staining material. Pleura, bronchi, and blood vessels on the section were not otherwise unusual.

Brain: The brain weighed 560 grams. Convolutions and sulci were not unusual. The brain was soft. Lateral ventricles were not dilated, and contained no blood. After one week's fixation, serial coronal sections revealed no evidence of hemorrhage, tumor, or infection.

Microscopically, the central nervous system sections showed lesions involving the white matter of the cere-

bral cortex, the cerebellum, and the brain stem (Figs. 2 and 3). The predominant feature showed almost complete demyelinization of the white matter with some preservation of the "U" fibers beneath the cortex. Axons were swollen and fragmented, with myelin being almost completely destroyed. Large numbers of gitter cells and hypertrophied astrocytes were scattered through the involved areas, sometimes collected in small foci of malacia and occasionally present around vessels. The gray matter ex-

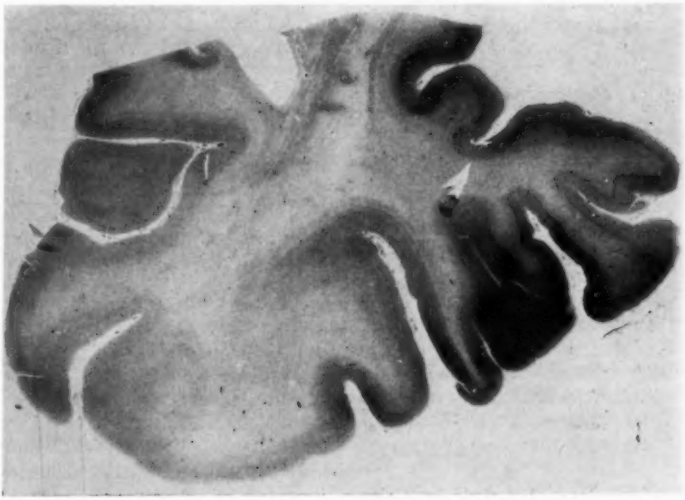

Fig. 2.—Section of cerebrum showing extensive demyelinization. (Lilly stain, ×2.)

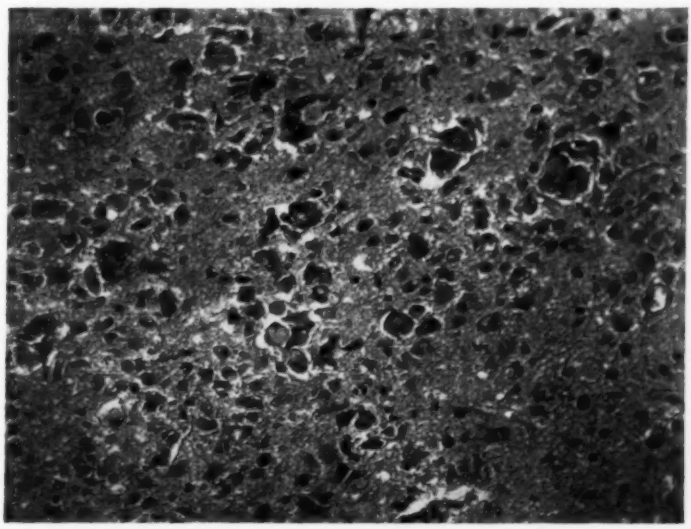

Fig. 3.—Section taken from brain stem showing swollen astrocytes and gitter cells. (H & E stain, ×470.)

hibited an essentially normal histology, there being only moderate gliosis in levels adjacent to the white matter. The meninges contained scattered small foci of lymphocytes, and in the brain there were occasional perivascular collars of lymphocytes. These inflammatory cells were regarded as secondary reactive elements. No true meningitis was observed.

COMMENT

The accurate antemortem diagnosis of a specific type of demyelinating encephalopathy is fraught with confusion, as various descriptions in the medical literature will reveal, despite the fact that several of these disorders are fairly clear-cut pathological entities. The variations of the process discussed include the acute infantile form of Krabbe, the subacute juvenile form of Scholz, and the chronic late form of Pelizaeus-Merzbacher. The term "diffuse sclerosis" has been suggested by Josephy and Lichenstein as preferred to Schilder's disease, the category where all forms of the disease have formerly been placed.

Jervis has preferred the term "diffuse sclerosis" in his review of the multiple types and varied characteristics of the demyelinating encephalopathies. He notes that Krabbe's type has a uniform clinical course whereby the diagnosis may at times be made without autopsy. The other forms of diffuse sclerosis (including Scholz and Pelizaeus-Merzbacher) have protean manifestations complicating the clinical diagnoses.

Proper names have been assigned to many variations of this process, often apparently without sufficient histopathological evidence of existing differences. Differentiating factors as to the categories often have been dependent to a large extent on the age at onset, chronicity, familial characteristics, and the presence or absence of consanguinity. There have not been a sufficient number of any single group of cases with similarities within the group and differences from others to allow segregation as a distinct entity.

Lack of agreement as to what constitutes the complete clinical syndrome and histopathological picture in the overlapping descriptions leads one to conclude that all varieties may be observed, depending on the duration, heredity, chronicity, and histopathological features as variously seen in infants, children, and adults. The consensus seems to favor considering these conditions as histological deviations of the same basic pattern. Frequently the presenting features of one are present in others. These differences appear to be effected by the age at onset, acuteness or chronicity, clinical course, presence or absence of familial traits and consanguinity, and aberrations in the demyelinating process.

SUMMARY

A 6-week-old infant admitted because of bizarre central nervous system symptoms and convulsions died on the tenth hospital day several hours after a ventricular puncture.

The clinical course was marked by almost continuous convulsions which resisted attempts at control. Laboratory studies were essentially noncontributory except that the spinal fluid protein was unusually high with a normal sugar content. In retrospect the *M. tetragenes* was considered a contaminant, following histological examination of sections from the central nervous system.

The observation of such a case represents one of the earliest reported based on a brief review of the English literature.

Differential diagnoses of convulsions in the neonatal period in the absence of obvious cause should include this group of conditions with questioning directed toward familial traits and/or consanguinity.

Attempts at classification of the many types, frequently named after the individual or individuals who described the disease, have been carried out by numerous investigators.

DENTAL CARIES AMONG ELEMENTARY SCHOOL CHILDREN IN OREGON

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FROM a number of reports in the literature, it has been demonstrated that there are wide variations in the degree of susceptibility to dental caries among population groups living in various geographic regions of the United States.

The results of a number of studies on dental caries conducted in Oregon during the last six years revealed that school children born and reared in certain geographic areas of the state have a high susceptibility to this disease. For an explanation of this phenomenon, the possible influence of different environmental factors has been investigated and the results were reported in the literature.[1-4] However, the above-mentioned studies were confined only to children within a narrow age range, i.e., 14 to 16 years of age.

The present paper deals with the dental status of all the children attending the grade schools of Corvallis, a city located in the Willamette Valley region of Oregon. For this reason, these data are of importance because they present for the first time the dental caries experience of an entire elementary school population of a city in Oregon, and thus afford the opportunity for comparisons with similar large groups examined elsewhere regarding the prevalence of caries among grade school children.

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Presented at the spring, 1953, meeting of the Pacific Northwest Section of the International Association for Dental Research held in Portland, Ore.

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MATERIALS AND METHOD

The subjects included in the present study were the children of the elementary schools, four public and two parochial, of Corvallis. Altogether, dental examinations were given to 1,534 pupils between the ages of 5 and 12 years, inclusive. This number represents practically all of the children attending the grade schools of Corvallis. All of the children examined were of the white race.

The children were examined at their respective schools and the physical facilities were excellent in all of them. The dental examinations were performed by means of mouth mirror and explorers in good natural light combined with a dental spotlight. A chip blower was used to dry the teeth prior to the examination. All of the children were examined in a regular dental chair.

The dental findings were called out to an assistant who made appropriate markings on a specially designed dental record. The criteria of what was considered a carious lesion have been described in another publication.[1] All missing permanent teeth were assumed to have been lost because of caries, except in a few instances where the subject upon questioning stated other reasons, e.g., lost by accident. In such cases the missing teeth were not recorded.

All examinations were made by the author. This fact minimizes variations in diagnosis and adds uniformity to the collected material.

The past and present caries experience in the permanent teeth of the subjects was expressed in terms of DMF teeth (decayed, missing, filled), whereas the symbol def (decayed, extraction indicated, filled) was used to designate past and present caries experience in their primary teeth. A tooth both carious and filled was counted only once in the total DMF or def score.

It is generally agreed that in computing the caries experience rates in the primary teeth, a missing tooth is not taken into consideration because in many instances it is difficult to decide whether the tooth is missing because of caries or as a result of physiological exfoliation. As a result of this, the def rate is not as accurate as the DMF rate in expressing the total caries experience of the individual.

RESULTS AND COMMENTS

The material presented in Table I gives the distribution of children examined by age groups. The total number of subjects given dental examinations was 1,534 and each age group was represented by a fairly large number of children. The same table also presents the percentage of children in each age group having one or more teeth attacked by caries. Observations on permanent teeth were made on children between the ages of 6 to 12 years, inclusive, whereas for the primary teeth, observations were made only on children from the ages of 5 through 8 years. At the age of 6 years, 34.4 per cent of the children examined showed one or more permanent teeth attacked by caries. The percentage of children with caries increased to 98.6 at the age of 12 years. In other words, at the age of 12 years, only 1.4 per cent of the children examined were found to be caries-free in their permanent teeth.

TABLE I. NUMBER OF CHILDREN EXAMINED BY AGE GROUPS AND PERCENTAGE OF CHILDREN WITH CARIES IN PERMANENT AND PRIMARY TEETH

AGE IN YEARS (LAST BIRTHDAY)	NO. CHILDREN EXAMINED	PER CENT OF CHILDREN WITH CARIES	
		IN PERMANENT TEETH	IN PRIMARY TEETH
5	168	---	78.0
6	221	34.4	89.1
7	230	66.1	88.7
8	238	88.7	88.7
9	200	92.5	---
10	173	95.4	---
11	162	96.9	---
12	142	98.6	---
All ages	1,534		

Regarding the primary dentition of the subjects, 78.0 per cent of them showed one or more teeth attacked by caries at the age of 5 years. The percentage of children with caries in the primary teeth increased to 89.1 at the age of 6 years, and then it decreased to 88.7 per cent at the ages of 7 and 8 years.

Table II provides information on the caries experience in the permanent and primary teeth of the children by age groups. This is expressed in terms of DMF teeth, def teeth, and DMF first permanent molars per child. As can be seen from this table, the average number per child of permanent teeth (DMF) attacked by caries was 0.75 at the age of 6 years and it increased with chronological age to 6.82 DMF teeth at 12 years of age. In regard to the primary teeth, the aver-

age def rate per child at the age of 5 years was 4.48. At 6 years of age, the mean rate increased to 5.67 and then it decreased slightly at 7 and 8 years of age.

This decrease in caries attack rates in the primary dentition of the subjects, starting at the age of 7 years, may be explained mainly as the result of teeth which have been extracted because of caries and, therefore, are not counted in computing the def rate, and to a smaller degree because of the physiological exfoliation of the central and lateral incisor teeth which takes place between 6 and 8 years of age. However, by the age of 9 years, the physiological exfoliation assumes progressively a more prominent role in the decrease of caries attack rates.

first permanent molars was considered separately in order to see how much they contributed to the over-all caries experience of the school children included in this study. The results are presented in Table II in terms of DMF first molars per child by specified age groups. It is apparent from these data that the first permanent molars accounted for almost the entire over-all DMF rates of the subjects from the ages of 6 through 9 years. At the age group of 11 years, the first permanent molars contributed two-thirds of the average DMF teeth rate of the children, and at 12 years of age the contribution of this tooth toward the over-all DMF rate was about half.

The items comprising the total caries experience of the subjects included in

TABLE II. NUMBER OF DMF TEETH, DMF FIRST MOLARS AND DEF TEETH OF 1,534 SCHOOL CHILDREN OF CORVALLIS, ORE.
(Rates Are Expressed Per Child by Specified Age Groups)

ITEM SPECIFIED	AGE IN YEARS (LAST BIRTHDAY)							
	5	6	7	8	9	10	11	12
DMF teeth	---	0.75	1.70	2.73	3.82	4.28	5.17	6.82
DMF first molars	---	0.75	1.67	2.61	3.19	3.40	3.47	3.58
def teeth	4.48	5.67	5.60	5.32	---	---	---	--

From the data presented in Tables I and II, it is evident that the subjects included in this study experienced the highest caries attack rates in their primary teeth (percentage of children with caries and def teeth per child) at the age of 6 years.

The condition of the first permanent molars is of special interest in studying the problem of dental caries among school children. Since this tooth is exposed longer to caries-producing agents because of its early eruption in the oral cavity, its loss in early life impairs the development and function of a normal masticatory apparatus. For this reason, the condition of the

the present study, separately for permanent and primary teeth, are given in Tables III and IV by specified age groups. In general, the average number of filled teeth per child increases as the chronological age advances. At 6 years of age the average number of filled permanent teeth per child was 0.14 and increased to 3.70 at the age of 12 years. However, as can be seen from Table III, the dental needs of the children increased also with advance in age. Dental needs due to caries in the permanent teeth include unfilled cavities, missing teeth, and teeth indicated for extraction. In the primary teeth, the dental needs are

comprised of unfilled cavities and teeth indicated for extraction because of caries. It is evident from the data here presented that over half of the dental needs of the subject population have not been met. In general, Tables III and IV demonstrate the seriousness of the dental caries problem in children, that is, the disparity between the dental services received in the form of fillings and the unmet dental needs of the subjects.

attack rates of the Corvallis children are considerably higher than the rates observed among the children of Hagerstown, Md., and Nicollet County, Minn. On the other hand, they are more nearly like the rates found among the children of New Zealand, a country having high dental caries prevalence rates.[8]

The above findings are in agreement with the results of previous studies on dental caries conducted in Oregon dur-

TABLE III. COMPONENTS OF DMF TEETH OF SCHOOL CHILDREN OF CORVALLIS, ORE. (Rates Are Expressed Per Child by Specified Age Groups)

ITEM SPECIFIED	AGE IN YEARS (LAST BIRTHDAY)						
	6	7	8	9	10	11	12
Filled	0.14	0.40	1.16	1.65	2.25	2.88	3.70
Decayed	0.62	1.39	1.80	2.58	2.49	2.99	3.63
Missing (plus extraction indicated)	0.00	0.01	0.03	0.13	0.16	0.14	0.29

TABLE IV. COMPONENTS OF DEF TEETH OF SCHOOL CHILDREN OF CORVALLIS, ORE. (Rates Are Expressed Per Child by Specified Age Groups)

ITEM SPECIFIED	AGE IN YEARS (LAST BIRTHDAY)			
	5	6	7	8
Filled	2.07	2.29	2.57	3.00
Decayed	2.61	3.38	3.04	2.48
Extraction indicated	0.01	0.20	0.30	0.23

TABLE V. COMPARISON OF AVERAGE NUMBER OF DMF TEETH PER CHILD IN CORVALLIS, ORE.; HAGERSTOWN, MD.; NICOLLET COUNTY, MINN.; AND NEW ZEALAND

PLACE	AGE IN YEARS (LAST BIRTHDAY)						
	6	7	8	9	10	11	12
Corvallis, Ore.	0.75	1.70	2.73	3.82	4.28	5.17	6.82
Maryland	0.29	0.73	1.20	2.02	2.51	2.84	3.66
Minnesota	0.50	1.43	2.30	2.86	3.39	4.16	5.50
New Zealand	—	2.01	3.09	3.82	4.44	5.62	7.08

In order to compare the caries experience rates of the Corvallis children with similar groups examined in other places, Table V was constructed. The information presented in this table demonstrates the differences in caries attack rates (DMF teeth) of the children in Corvallis with those of the same age groups examined in Hagerstown, Md.,[5] Nicollet County, Minn.,[6] and New Zealand.[7] From these data it is shown that, in general, the caries

ing the last few years.[1, 3, 9] In these previous investigations it was shown that freshmen college students who were residents of the state and native-born and reared school children, 14 to 16 years of age, experienced high rates of caries attack when compared with those observed among subjects of the same age groups examined in other parts of the country.

The results of the present study, together with the findings of the pre-

vious investigations conducted in Oregon, strongly indicate the necessity for further research for the elicitation of the factors responsible for the high prevalence of dental caries observed among Oregon school children.

SUMMARY

A study was undertaken to ascertain the dental status of the elementary school children attending the public and parochial schools of Corvallis, Ore. Altogether, dental examinations were given to 1,534 children between the ages of 5 and 12 years, inclusive.

The results of this investigation may be summarized as follows: The percentage of children with one or more permanent teeth attacked by caries, as well as the DMF rate per child, increased with chronological age.

With regard to the primary teeth, the children of this study reached their highest point of caries experience (percentage of children with caries and def rate per child) at the age of 6 years.

An analysis of the components of the DMF and def rates revealed a great disparity between the dental needs of the subjects and the dental services received.

The caries experience in the permanent teeth of the school children included in this study was found to be higher in comparison with that of subjects of the same age groups examined in Maryland and Minnesota and was more nearly like that of the New Zealand school children.

The present findings provide additional evidence regarding the magnitude of the dental caries problem among the school children residing in this area of the Pacific Northwest.

Appreciation is expressed to Dr. W. L. Van Loan, Superintendent of Public Schools, and to the principals and teachers of the public and parochial grade schools of Corvallis, Ore., for their kind assistance and cooperation in this study.

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LEUKEMIA IN AMERICAN SAMOA

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THERE have been few reported cases of leukemia among the Polynesians in the South Pacific. This may be due to a lack of interest in the disease in the South Pacific area, or to the belief by some authorities that leukemia does not occur among the Polynesians, but is more likely due to a scarcity of physicians and trained laboratory personnel. Strong[1] states, "Apparently only the myelogenous has been reported in the tropics and this form rarely." Manson-Bahr[2] devotes one and a half lines to leukemia in his textbook on *Tropical Diseases*.

Any discussion of Polynesians brings forth the following essential questions: Who are the Polynesians? Where did they originate? How pure are the Polynesians? Most anthropologists believe them to be basically Malayan having reached the Polynesian triangle by "island hopping" eastward. Some anthropologists have also suggested that they migrated by way of Siberia, North and South America, and then "island hopped" westward from South America. It is difficult to give an exact definition of a pure Polynesian, i.e., Samoan. Keesing[3] in his book *Modern Samoa* states, "The percentage of 'pure' Samoans is without doubt proportionately small" and that ". . . the pure Polynesian stock is likewise going out of existence everywhere." Bell[4] points out that since the sixteenth century there have been many European expeditions of one type or another to the South Pacific, and the hospitable friendly customs of the Polynesians fostered amicable relations with the visitors. Two world wars brought millions of Europeans and Americans to the South Pacific, and as a result even the purest of the Polynesians were subject to cross-breeding; however, Buck[5] comments, ". . . a statement has been made in an official government handbook that the Samoans are the purest branch of the Polynesians."

A review of the Navy Annual Reports, Samoan Hospital, American Samoa,[6] from 1928 to 1951, makes no mention of leukemia until 1938 when one case of myelogenous leukemia was reported as the cause of death in a patient between 10 and 20 years of age. The diagnosis was made on a blood smear, but there was no record of a sternal puncture or autopsy having been performed. In 1945 one case of acute lymphatic leukemia was reported as the cause of death in a 3-year-old Samoan female, the case having been diagnosed by blood smear and autopsy. The child's mother was from Hawaii and is reportedly part Japanese. In 1949 another case of acute lymphatic leukemia in a 12-year-old Samoan male was reported as the cause of death, the diagnosis having been made by blood smear and autopsy. The boy's father was from the Tongan Islands which are south

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of American Samoa. In 1952 there was one case of myelogenous leukemia in a 35-year-old, half-caste Samoan female which was diagnosed by blood smear and autopsy. On Dec. 31, 1952, a 16-year-old Samoan male was admitted with a diagnosis of rheumatic fever and later diagnosed as acute myelogenous leukemia by blood smear and sternal puncture. The patient died on April 6, 1953. He was supposedly "pure" Samoan.

In a review of 25,000 hospital admissions and 1,433 death certificates, no other suspicious cases of leukemia were found.

CASE REPORTS

CASE 1.—I. M., a 16-year-old Samoan male, was admitted to the hospital Dec. 31, 1952, with a diagnosis of rheumatic fever. His chief complaints were attacks of palpitation, breathlessness, and dizziness. These symptoms were first noted by him in October, 1952, and had become increasingly more severe. He could not be persuaded to seek medical advice until the time of his admission. There was no history of joint involvement. The physical examination on admission revealed the following: pallor of the skin and mucous membranes, enlargement of the heart to the left, a soft systolic murmur, 3 × 3 cm. ulcer on upper third of right tibia, spleen and liver not enlarged. There was no lymphadenopathy noted.

X-ray of chest on Jan. 2, 1953, showed lung fields clear, heart mitral configuration. Laboratory findings were as follows: Jan. 2, 1953, hemoglobin 4.7 grams, red blood count 1,400,000, white blood count 10,000. No differential count. Urinalysis was negative; stool examination revealed *Trichuris trichura*. Course in hospital was as follows: Patient received numerous blood transfusions, 300,000 units of procaine penicillin daily, one course of ACTH for eleven days (12.5 units every six hours). The white cell count varied between 10,000 and 35,000 with a high percentage of immature white cells present during the last few counts. On March 10, 1953, a sternal puncture was done which confirmed the diagnosis of myelogenous leukemia. On March 30, 1953, the patient's father signed a release and took his son home where he expired seven days later (April 6, 1953).

CASE 2.—(From the Navy Hospital and autopsy records.) K. T., a 12-year-old Samoan male, was admitted to the hospital Oct. 10, 1949, for medical observation. His chief complaints were pain in the chest and anorexia of three days' duration. His parents stated that he had been perfectly well until three days prior to admission. On physical examination, the patient was in acute distress; there was pallor of conjunctiva, diminished breath sounds over both bases with moist crepitant râles over this area; tachycardia was present; liver and spleen were not palpable due to epigastric tenderness. The patient expired eight hours after admission. Autopsy report: Hemorrhagic petechia, visceral pleura of both lungs; multiple small infarct left lower lobe; liver, twice normal size; spleen, four times normal size, fibrotic areas, left lower pole; scattered petechia over both kidneys. Microscopic diagnosis, acute lymphatic leukemia.

CASE 3.—(From the Navy Hospital and autopsy records.) L. K., a 3-year-old Samoan female, was admitted to the hospital Nov. 12, 1944, because of severe epistaxis, weakness, and loss of weight. The physical findings were pallor, and palpitation of the heart; the liver and spleen were not palpable on admission. The white blood count varied from 5,600 to 108,000 and the lymphocytes from 59 to 92 per cent. The red blood count showed a progressive anemia in spite of repeated blood transfusions. The temperature was high and septic in type. The liver and spleen became palpable, and the

patient expired on Jan. 17, 1945. The autopsy report was acute lymphatic leukemia.

The average reported deaths from various kinds of leukemia in Western Samoa (Trust Territory of New Zealand, population, approximately 80,000) are three per year.[7]

SUMMARY

1. Acute lymphatic leukemia and myelogenous leukemia do occur among the Polynesians, i.e., Samoans.

2. It is difficult to define a pure Polynesian, i.e., Samoan.

3. Two cases of acute lymphatic leukemia and two cases of myelogenous leukemia proved by sternal puncture or autopsy are reported.

I wish to thank Dr. Sidney Farber of the Children's Cancer Research Foundation, Boston, Mass., for confirming the diagnosis made in Case 1 by blood smear and sternal puncture.

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GAMMA GLOBULIN DOSAGE AND MEASLES CONTROL

Report of 188 Cases

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MEASLES modification has been of interest to me since my preliminary report on the use of parent's blood serum in 1927,[1] which followed Karelitz and Levin's report[7] earlier the same year. In two later reports Dickson and I[2, 3] reported the use of pooled adult serum at Grady Hospital and in private patients with good results. We attained more complete protection than modification. At the Grady Hospital where the purpose was to stop measles in the wards we treated seventy-eight children within four days of exposure. Sixty-two of these were protected, and of the remaining sixteen who had modified measles, eleven had received less than 0.5 c.c. per pound. In one ward a group of thirty received complete protection with a dosage of 0.5 c.c. per pound* when given within four days after exposure. If gamma globulin is concentrated twenty-five times, the above dosage of serum would represent 0.02 c.c. per pound. The above reports include six children given serum for therapeutic purposes early in the disease with apparent modification in five. Dosage was 1+ c.c. per pound.

MEASLES ENCEPHALITIS TREATED WITH PLASMA

In the years following these early reports and before the advent of gamma globulin I have treated three patients with postmeasles encephalitis with large doses of plasma. Two cases were moderately severe but the patients had rapid recoveries. One case was extremely severe; the patient was unconscious for several weeks and his prognosis was extremely grave. It seemed at the time that all treatment was unavailing, but much to the surprise of everyone he recovered after one or two bouts of prolonged convulsions. He seems a normal boy four years later, whose mental and physical progress has been normal to date. Certainly the small number of cases have little significance, but in view of the lack of specific therapy I would use plasma again in severe postmeasles encephalitis.

GAMMA GLOBULIN

In a group of approximately 200 children given gamma globulin for measles modification there were 188 on whom sufficient data were available for analytical study. All were private patients seen between 1949 and 1952, inclusive. The data were taken from their charts with some cooperative help from the mothers.

The optimum dosage was assumed to be 0.025 c.c. per pound within four days of exposure. Our results would seem to indicate a need for revision of that figure. A corresponding dose of plasma would be 0.625 c.c. per pound, and as previously shown many received complete protection rather

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*One of the two donors was known to have a serum of high potency.

than modification. Barondess,[4] in a recent study on the status of gamma globulin, summarizes the reports of Stokes, Janeway, Ordman, Jennings, Maris, and Gellis and suggests a dosage of 0.02 c.c. per pound for attenuation and 0.08 c.c. per pound for protection. In the summary of an exhibit by Janeway and Piersma[5] it is brought out that gradually increasing dosage in intimate exposures resulted in complete protection in 86 per cent of contacts. The dosage recommended in this study was 0.02 c.c. per pound for modification and 0.1 c.c. per pound for complete protection.

In my cases there were 102 patients who developed modified measles and 86 who did not develop measles. Of those developing modified measles there were 89 on whom there are sufficient weight data for analysis. Of these, 30 were above the optimum dosage of 0.025 c.c. per pound. Of the 86 who did not develop measles, there were 79 on whom there were weight data, and of these, 51 were given more than the optimum dosage.

Of 89 patients developing measles, 54 were sibling contacts without regard to dosage, whereas of the 86 who escaped measles, only 6 were sibling contacts.

Of 89 developing measles, 35 were nonsibling contacts with an average dose of 0.025 c.c. per pound. Of the sibling contacts (54), the dosage was 0.0276 c.c. per pound.

Of those who escaped measles (86) there were 79 nonsibling contacts with an average dosage of 0.035 c.c. per pound.

COMMENT ON DOSAGE

It would seem that if one seeks modification of measles with gamma globulin an important factor in determining the optimum dosage is whether or not contact is sibling or nonsibling, for in this series 54 out of 60 sibling contacts developed measles although the average dose of gamma globulin was higher than in nonsibling contacts.

Of 86 who escaped measles there were only 6 sibling contacts.

For Modification, Suggested Dosage
Nonsibling contacts: 0.015 to 0.02 c.c. per pound.
Sibling contacts: 0.025 to 0.03 c.c. per pound.

For Protection (Rarely Indicated in Private Patients)
Nonsibling contacts: 0.05 to 0.07 c.c. per pound.
Sibling contacts: 0.075 to 0.125 c.c. per pound.

The above dosage schedule should apply within five days after contact.

All gamma globulin in this series was Red Cross gamma globulin.

IMMUNITY AFTER GAMMA GLOBULIN

In the long period of observation since 1927 I have seen only an occasional second attack of very mild type which is in keeping with Karelitz's[6] opinion that modified measles usually confers lasting immunity.

Of the 86 escaping measles in this series there were 21 who developed measles from a subsequent exposure. Ten of these had modified measles and eleven were severe. So it would seem that some immunity is acquired in about half who escape measles from the original exposure when protected by gamma globulin.

Recurrent Measles.—In this group there was one family of three children in whom measles occurred twice. One child had not had gamma globulin after either exposure, and the two others had modified measles, the first attack after gamma globulin.

One other child in this series had moderately severe measles on two occasions without gamma globulin either time.

Thus it would seem that there is an occasional family in whom measles does not confer the usual immunity.

Complications.—No complications were observed in any of the children of this series who had had gamma globulin nor in the previous cases protected by adult blood serum.

COMMENT

It would seem that there is a tendency to overtreat by giving too much gamma globulin where measles modification is desired. Body weight is a more accurate method of obtaining dosage requirements than age. The time after exposure is important in the dosage schedule, the requirements increasing rapidly after the fourth day of contact but where modification is desired rarely exceeding 0.05 c.c. per pound even late in the postcontact period. Deliberate overdosage would seem justifiable in stopping hospital epidemics.

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ENCEPHALITIS IN CHILDREN WITH MEASLES WHO WERE GIVEN ATTENUATING DOSES OF GAMMA GLOBULIN

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THE administration of gamma globulin for the attenuation of measles is now a widespread practice. While this procedure will be effective in attenuating most cases of measles, occasionally complications as encephalitis or encephalomyelitis will occur. This paper presents three instances where this was observed at our hospital.

Two cases have already been reported where encephalitis developed although the patients received attenuating doses of gamma globulin. The first case, described by Smith,[1] was that of a 19-month-old infant who received 0.6 c.c. of gamma globulin nine days before the rash developed. One day after the appearance of the rash there were marked neurological signs and a pleocytosis of the cerebrospinal fluid (140 cells per cubic millimeter, mostly lymphocytes). The child was given 6 c.c. of gamma globulin and was discharged on the third hospital day. Ten days later she was entirely well. Smith believed that the encephalitis was attenuated due to the prophylactic dose of 0.6 c.c. of gamma globulin. The second case is that of Rosenzweig and Klugh[2] who reported that a 3-year-old child (35 pounds) was given 2.0 c.c. of gamma globulin twelve days before the rash appeared. Two days after the onset of the rash the patient was admitted to the hospital with marked neurological signs. The cerebrospinal fluid revealed 176 cells per cubic millimeter, mostly lymphocytes. The child was discharged after the second hospital day. Examinations one week and one month after admission showed that the child made a complete recovery.

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CASE REPORTS

We observed three similar cases. It was the patients' parents who informed us that attenuating doses of gamma globulin were administered prior to admission.

CASE 1.—A 6-year-old boy was admitted in May, 1948. He received gamma globulin (amount not noted) eleven days before admission. Nine days prior to admission the rash appeared and lasted for two days. The child was considered to have recovered from the measles and was up and playing about. He complained of a headache the following morning. Afterward, he vomited daily several times a day. He was admitted to the hospital because of projectile vomiting, lethargy, and neurological signs. On admission he was drowsy but was easily aroused. The left pupil was irregular and smaller than the right. There was a marked Kernig on the left. The cerebrospinal fluid revealed 250 cells per cubic millimeter, lymphocytes predominating. He was afebrile on admission and throughout his hospital stay. The patient was dis-

charged after seventeen days in the hospital, completely well.

CASE 2.—(May 1952) A 10-year-old boy weighing 90 pounds was given 4 c.c. of gamma globulin at the onset of the measles rash. He ran a spiking temperature that rose to 105° F. Five days after the appearance of the measles rash he had convulsions and developed signs of encephalitis. On admission the pupils were dilated and the eye grounds showed vascular engorgement. There were nuchal rigidity, hyperactive deep tendon reflexes and bilateral Babinski. The cerebrospinal fluid contained 195 cells per cubic millimeter, mostly lymphocytes, 65 mg. total protein per 100 ml., a faint trace of globulin, and an inorganic phosphorus of 1.9 mg.[3] per 100 ml. He was treated with 46 c.c. of gamma globulin and adjunctive therapy (described in detail in another paper[4]). He was discharged after a hospital residence of six days. A follow-up examination seven weeks later showed that he made a complete recovery.

CASE 3.—(May 1952) A 5-year-old boy received 2 c.c. of gamma globulin seventeen days prior to admission. Four days before admission he developed a faint rash. He was admitted to the hospital because of "loss of consciousness." This patient was spastic and mentally retarded. He was in stupor; the deep tendon reflexes were hyperactive; and the Babinski was positive bilaterally. His cerebrospinal fluid showed 57 cells per cubic millimeter, lymphocytes predominating; the total protein was 47 mg. per 100 ml.; there was a very faint trace of globulin; and the inorganic phosphorus of 1.9 mg.[3] per 100 ml. He was given adjunctive therapy (described in detail in another paper[4]), and discharged after five days in the hospital. At a follow-up examination his parents stated that his physical and mental conditions were unchanged and were the same as before the encephalitic infection.

DISCUSSION

It is probable that the number of our cases might have been larger had we contacted the private physicians of other patients admitted to this hospital for measles encephalitis and encephalomyelitis. We did not think it necessary to do this because it is evident that attenuating doses of gamma globulin will not prevent encephalitis; it is clearly indicated that children with measles should be observed for signs of central nervous system involvement whether or not they received attenuating doses of gamma globulin. We are in complete accord with Rosenzweig and Klugh[2] who stated that the example of their case "should serve to make us feel less complacent regarding the possibility of the occurrence of a serious complication."

The question arises as to why encephalitis and encephalomyelitis should develop in children with measles who were given gamma globulin for attenuation. In discussing the etiology of encephalitis and encephalomyelitis in measles, Odessky and associates[4] have proposed several hypotheses to explain the occurrence of these central nervous system complications. Making allowance for the administration of attenuating doses of gamma globulin, whereby a quantity of antibodies to the virus or viruses of measles are injected, the hypotheses of Odessky and co-workers have been modified as follows:

1. From clinical observations reported in the literature and from the above cases, it has been established that the dose for attenuation will not prevent the occurrence of measles. Therefore, the measles virus, still pres-

ent, may reincubate and subsequently produce central nervous system complications.

2. The administration of 2 to 4 c.c. of gamma globulin will produce only a small rise in the gamma globulin level of the blood (Bruton[5]) so that for a small percentage of measles cases this dose may not be adequate.

3. Because of a poor nutritional state, fever, or general debility from the measles infection, the hematoencephalic barrier becomes weakened, or more permeable, thereby enabling the virus to invade the central nervous system even though an attenuating dose of gamma globulin was administered.

4. The patient may not have the physical capacity for acquiring active immunity as readily as most of the measles cases, that is, he cannot produce sufficient antibodies fast enough over and above the quantity of antibodies supplied by the attenuating dose of gamma globulin.

5. In rare instances the patient cannot establish acquired immunity at all. An illustration of this condition is the case of agammaglobulinemia recently described by Bruton.[5]

SUMMARY AND CONCLUSIONS

1. Three cases are described in which encephalitis complicated measles although attenuating doses of gamma globulin were administered.

2. Several hypotheses are presented to explain the occurrence of encephalitis following an attenuating dose of gamma globulin.

3. It must be kept in mind that attenuating doses of gamma globulin will not assuredly prevent the development of encephalitis and encephalomyelitis in measles.

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EXTRAVESICAL URETERAL ECTOPIA

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ECTOPIC ureter opening extravesically is a rather rare anomaly; Crenshaw and Buchtel[1] reported its incidence at the Mayo Clinic in 1936 as being 1:81,150. In recent years more and more cases have been reported. In 1949, when Burford and associates[2] reviewed the literature, 425 cases were found. In the last 154 cases reviewed by them, females outnumbered males 5 to 1. Since that time several additional reports have appeared.[3, 4]

In the female the ectopic opening may occur in the following locations listed in order of frequency: vestibule of vagina, urethra, vagina, cervix or uterine cavity, and Gartner's duct. In the male, listed in order of frequency, it may open into the posterior urethra, seminal vesicle, prostatic utricle, ejaculatory duct, and vas deferens. In either sex the opening may rarely be in the rectum.[2] Commonly, upon investigating the upper urinary tract, reduplication of the pelvis and ureters is found, with the ectopic orifice most frequently being from the upper pole. However, both ureters of a duplication have entered ectopically, as have ureters from normal kidneys, solitary kidneys, and kidneys the site of other types of anomalous development.[5] There is no predilection as to the side involved, and the lesion may occur bilaterally.

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These disorders are usually manifest early in life. The diagnosis may be overlooked, but persistence of symptoms with consequent social maladjustment, and actual physical disability, makes complete urological investigation mandatory. In order to re-emphasize the clinical picture and findings, we have reviewed our series of cases.

CASE REPORTS

CASE 1.—E. J. (U.H. 175-827), female, aged 23 years, was admitted with a history of incontinence, associated with normal voiding, since birth. Routine examination and laboratory data were noncontributory. At cystoscopy, an aberrant ureteral orifice was located at the urethral meatus. This proved to be from the hydronephrotic upper half of a reduplicated right kidney. The left kidney was normal. Right heminephrectomy was carried out with cure of the incontinence and preservation of a functioning lower right kidney.

CASE 2.—P. A. (U.H. 294-919), female, aged 15 months, was admitted with the chief complaint of recurrent fever and pyuria, controlled by antibiotic therapy. A white purulent vaginal discharge had been noted shortly before admission. Physical examination revealed only tenderness in the left upper quadrant. Pyelography showed a normal right kidney. On the left a large, soft tissue mass was seen above a depressed lower pelvis. At cystoscopy an aberrant ureteral orifice on the posterior lip of the urethra led to a large, hydronephrotic, upper left pelvis. Nephrectomy was carried out since an anomalous blood

supply prevented sparing the lower portion of the kidney.

CASE 3.—T. C. (U.H. 228-788), female, aged 13 years, was similarly admitted with the history of lifelong incontinence associated with normal micturition. Physical examination and laboratory data were noncontributory. At cystoscopy, posterior to a normal urethra, on the vestibule of the vagina, an aberrant ureteral orifice from a slightly hydronephrotic, upper

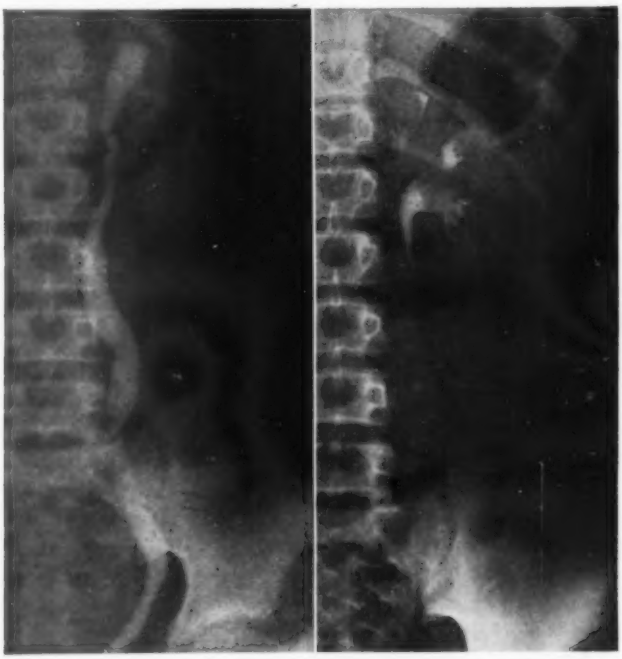

Fig. 1 (Case 3).—Retrograde pyelograms showing the hydronephrotic upper pelvis (left) contrasted with the appearance on excretory urography (right).

reduplicated left kidney was found. The right kidney was normal. (Fig. 1.) Heminephrectomy was carried out with relief of symptomatology.

CASE 4.—S. W. (U.H. 276-599), female, aged 7 years, was admitted with the chief complaint of incontinence associated with normal voiding. At cystoscopy, within the urethra an ectopic orifice was found leading to a reduplicated upper left pelvis. The right kidney was normal. (Fig. 2.) Heminephrectomy was without incident, and the condition was cured.

CASE 5.—E. L. (U.H. 136-699), female, aged 36 years. This patient was admitted with the chief complaint of left flank pain. Patient had had slight urinary leakage all of her life, incompletely corrected by a plastic gynecological procedure to the urethra four years previously. Pelvic examination revealed a cystic swelling in the left fornix. At cystoscopy, reduplication on the right was found. On the left, a soft tissue mass was noted above a depressed renal pelvis. Although no aberrant orifice was found preoperatively, left heminephrectomy was carried out with cure of the symptomatology.

CASE 6.—A. J. (U.H. 131-612), female, aged 16 years, was admitted because of persistent urinary leakage

with a resulting excoriation of the vulva. Initial cystoscopy revealed only the right ureteral orifice to be normally positioned. External and to the left of the urethra, however, a vestibular opening was found leading to an infected left hydronephrotic kidney. At operation, a double kidney was found and removed completely because of the involved blood supply.

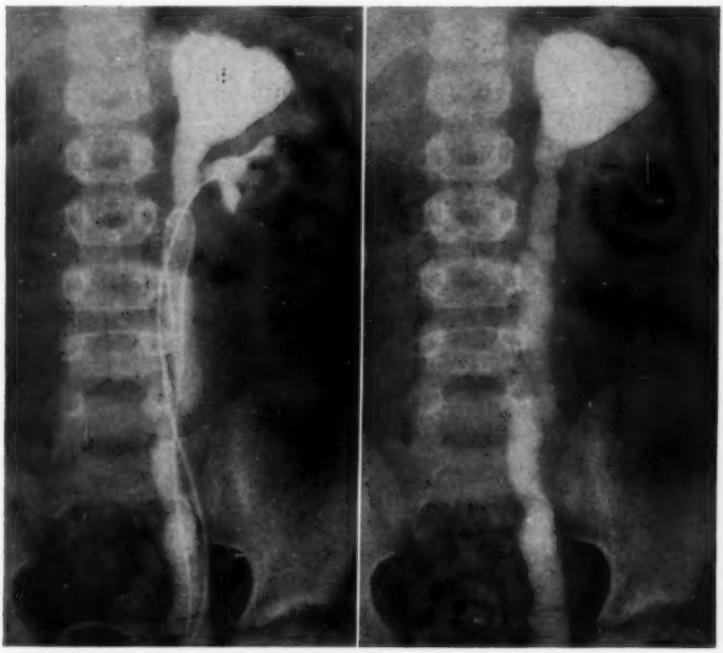

Fig. 2 (Case 4).—The hydronephrotic, ectopic ureter and kidney are demonstrated by retrograde pyelography on the right. On the left is superimposed the normal lower half of the reduplication.

Postoperatively the urinary leakage continued. A second cystoscopy then revealed a second aberrant opening just within the urethral meatus, leading to a previously undiagnosed reduplicated right kidney. Right heminephrectomy led to complete continence.

Case 7.—M. H. (U.H. 156-582), female, aged 56 years, had had attacks of right flank pain and pyuria since childhood. She had lifelong incontinence associated with a purulent urethral discharge. A gynecologist in another city had incised a vaginal mass shortly before entry here, which led to increased leakage. At cystoscopy, an aberrant ureter was found at the site of the previous incision and drainage in the anterior vaginal wall. A normal lower right kidney was found beneath the hydronephrotic upper half. The left pelvis showed complete reduplication. (Fig. 3.) Nephrectomy was carried out because of the involved vascular pattern. There was no subsequent incontinence.

Case 8.—D. H. (U.H. 256-499), male, aged 7 years, was transferred to the genitourinary service from pediatrics for study of a left hydronephrosis found in the routine investigation of a febrile episode. A small right kidney was visualized on excretory urograms. After repeat cystoscopies had elucidated the nature of the ob-

structing ureterovesical stricture on the left, careful search finally led to the finding of an ectopic right ureter opening into the prostatic urethra. Left ureteroneocystostomy following nephrostomy alleviated the recurrent febrile episodes. The right ureter was undisturbed since there was no incontinence.

duct. Nephrectomy was followed by cure of symptomatology.

DISCUSSION

The ureter develops as a bud from the Wolffiian duct. This bud grows cranially to join the metanephric mass; caudally it is drawn with the

Fig. 3 (Case 7).—Bilateral reduplication with the ectopic, reduplicated, upper right pelvis showing hydronephrosis and hydroureter.

CASE 9.—C. L. (C.G.H. 6284), male, aged 27 years. This white soldier had been transferred to the Zone of the Interior because of persistent pyuria, and recurrent pain in the right flank. He had had a previous left ureteral calculus removed overseas. At cystoscopy it was possible to demonstrate the nonfunctioning right kidney by catheterizing the right ejaculatory

Wolffian duct to form the trigone of the urinary bladder and the normally positioned ureteral orifice. Splitting of the ureteral bud will result in reduplication of the pelvis or upper ureter whereas the presence of two buds will eventuate in complete reduplication. If the ureteral buds lie

close together on the Wolffian duct it is likely that they will enter side by side in the urinary bladder. When the buds are more widely separated the ureter from the upper bud may be carried extravesically in the expansion of the caudal portion of the Wolffian duct as it forms the trigone, resulting in ectopia of that orifice. In the male the Wolffian duct ends in the posterior urethra as the opening of the ejaculatory duct, and in its process of expansion forms the seminal vesicles and vas deferens. In the female the duct opens onto and contributes to the formation of the vestibule; cranially it extends as Gartner's duct along the anterior and lateral vaginal wall, through the substance of the cervix and uterus into the broad ligament to the parovarium or Rosenmüller's nodule.[6]

The symptoms of extravesical ureteral ectopia differ with the sex. Among females the most frequent complaint is leakage of urine independent of normal micturition. Leakage in other cases may occur under stress such as coughing or sneezing; it may be present only during the day or night. When infection is present the lesion may be manifested by a purulent discharge, or chills, fever, and flank pain. The condition in males has been diagnosed less frequently, because the ectopic site is always above the external sphincter; incontinence, therefore, is not a part of the symptomatology. Symptoms in the male are variable but are most frequently those arising from chronic ureteral obstruction resulting in hydronephrosis. Dull flank pain or persistent pyuria with or without fever may be present.

Intravenous pyelography is of considerable help in making the diagnosis. Here may be seen reduplication of the pelvis and ureter with or without dilatation of the upper segment. If marked destruction of the kidney subsequent to obstruction has taken place, there may be failure to visualize the upper portion of a double kidney or of the entire kidney if duplication is not present. When the lesion is suspected an attempt at identification and catheterization of the ectopic orifice should be made. The openings are usually small, difficult to find and to catheterize. Identification can sometimes be aided by the intravenous injection of indigo carmine. In cases of suspected uterine or vaginal opening, a sponge can be left in the vagina for evidence of discoloration.

At operation where reduplication is present the ureter to the upper portion usually lies posterior to the vessels. Frequently there is a separate blood supply to each portion, thereby facilitating heminephrectomy which is certainly the operation of choice. Occasionally the ureter may be anastomosed to the bladder particularly if it is necessary to preserve as much renal parenchyma as possible. In some cases because of the vascular distribution to the affected kidney, nephrectomy must be done. Although excision of the ureteral stump is not necessary in all cases, occasionally if markedly dilated and infected it may be the source of a persistent irritative discharge unless removed.

These cases represent the accumulated experience of this clinic during the last twenty years. There were seven female cases and two males. The females were all seen because of incontinence. Pyuria was a constant

finding. The females all had reduplications on the involved side. There was bilateral reduplication of the urinary tract in three of the seven female cases. In Case 6 both upper portions of the reduplicated kidneys had aberrant orifices. In the females, therefore, there was a total of eight ectopic ureters. One of these could not be located, two were found at the urethral meatus, two were found within the urethra, two were located on the vestibule, and one on the anterior vaginal wall.

The persistence of incontinence into middle age in Cases 5 and 7 points up the need for early and adequate study. Both patients had been subjected to gynecological procedures which did not attack the primary disease.

In both males the kidneys bilaterally were unduplicated. Case 8 was an incidental finding, with the hypoplastic kidney emptying into the prostatic urethra. This lesion has been described by others.[7] The findings in Case 9, similarly a urological curiosity, have been discerned clinically in only a few instances.[3] Both patients initially were studied because of contralateral disease; both had persistent pyuria.

SUMMARY

Nine cases of extravesical ureteral orifice are reported. The embryology, symptomatology, and clinical picture are described. The necessity for complete urological study in cases of incontinence or pyuria is emphasized, especially incontinence associated with normal voiding.

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THE USE OF MYSOLINE IN THE TREATMENT OF EPILEPSY

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IN 1949, Bogue and Carrington[1] demonstrated that Mysoline* (5-phenyl-5-ethyl-hexahydropyrimidine-4: 6-dione) protected animals against electrically or chemically induced convulsions. The first clinical investigation, dealing with the use of this drug in the treatment of epilepsy, was presented by Handley and Stewart[2] in 1952. They reported that Mysoline was an effective drug for the control of major motor epilepsy and that it was essentially nontoxic. The present paper deals with a group of epileptic patients, mostly children, of the Johns Hopkins Hospital who were treated with Mysoline.

MATERIAL FOR STUDY

Mysoline was administered to 100 patients who suffered with frequent epileptic seizures of various types. Eighty-one of these patients had been receiving maximum dosages of one or more anticonvulsants such as phenobarbital, Mebaral, Dilantin, Mesantoin, Paradione, or Tridione for at least one year before the Mysoline was prescribed. In each instance, the previous medication had proved to be ineffective. Each of these eighty-one patients initially was given Mysoline in addition to the same dosage of the previous ineffective medication. In forty-two of these eighty-one patients, the previous ineffective medication was gradually withdrawn after the patient had been receiving Mysoline for at least two months. The remaining thirty-nine patients continued to take both the previous medication and the Mysoline throughout the entire observation period.

Nineteen of these 100 patients who had never received any type of anticonvulsant therapy were given Mysoline alone.

Sixty-four patients suffered with cryptogenic (idiopathic) epilepsy and thirty-six with secondary (organic) epilepsy. Fifty-one had major motor (grand mal) seizures, nine had petit mal (simple staring) spells, five had psychomotor seizures, eleven had minor motor (akinetic or myoclonic) spells, and twenty-four had two or more of the various types of seizures (mixed epilepsy). We reserve the term petit mal for those spells which consist essentially of transient lapses of consciousness associated with bilaterally synchronous three per second spike and wave forms in the electroencephalogram. By minor motor spells we mean akinetic or myoclonic attacks of momentary duration.

Sixty-eight of our patients ranged in age from 2 to 14 years and thirty-two were over 15 years of age.

DURATION OF TREATMENT AND DOSAGE

The duration of Mysoline therapy ranged from three months to one

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*Mysoline is being jointly investigated by Ayerst, McKenna and Harrison Ltd., and Imperial Chemical (Pharmaceuticals) Ltd.

year. Forty-three patients have been receiving the drug for ten or more months.

Mysoline is supplied in 250 mg. tablets. The dosage of the drug administered to our patients varied from 375 mg. daily to 1.5 Gm. daily as shown in Table I. In each case the medication was administered in two to four doses over the course of the day.

1. Controlled: no recurrence of seizures during the entire observation period.
2. Markedly improved: number of seizures reduced to less than one-fourth of previous frequency.
3. Improved: number of seizures reduced to between one-half and one-fourth of previous frequency.
4. Failure: number of seizures only very slightly reduced, the status remained the same, or the seizures became more frequent.

TABLE I. DOSAGE OF MYSOLINE

AGE	INITIAL DOSAGE	MAXIMUM DOSAGE
Under 6 years	125 mg. three times a day	250 mg. four times a day
Over 6 years	250 mg. two times a day	500 mg. three times a day

TABLE II. RESULTS OF MYSOLINE THERAPY IN FORTY-TWO PATIENTS WHO HAD BEEN REFRACTORY TO OTHER ANTICONVULSANT DRUGS

TYPE OF SEIZURE	NO. OF PATIENTS	CONTROLLED	MARKEDLY IMPROVED	IMPROVED	FAILURE
Major motor (grand mal)	23	14	3	1	5
Petit mal	4	0	0	0	4
Psychomotor	1	0	0	0	1
Minor motor	5	0	0	0	5
Mixed* (major motor and petit mal)	4	0	2	1	1
Mixed* (major motor and psychomotor)	2	0	1	1	0
Mixed* (major motor and minor motor)	3	0	2	1	0
Total	42	14	8	4	16

For the first two months, these patients received the previous ineffective medication in addition to Mysoline. Thereafter, they received Mysoline only.
*Only the major motor seizures were favorably affected in these cases.

RESULTS

All of our patients had suffered with frequent seizures (daily or weekly) prior to the onset of Mysoline therapy. The results of treatment were assessed by comparing the number of seizures which occurred during the course of Mysoline therapy with the number of seizures which had occurred during a similar interval of time just prior to the onset of Mysoline therapy. In evaluating the response to therapy, the following classification was employed.

Sixty-three (63 per cent) of our 100 patients were benefited by Mysoline therapy: the seizures were entirely controlled in 30 (30 per cent), the number of seizures were markedly reduced in 20 (20 per cent), and moderately reduced in 13 (13 per cent). The administration of Mysoline did not favorably affect the patients' condition in the remaining thirty-seven patients.

As is shown in Tables II, III and IV, Mysoline was effective only in the treatment of major motor epi-

lepsy: the attacks were completely controlled in 30 (61 per cent) of our forty-nine patients who suffered with pure major motor seizures. None of our patients who had other types of seizures (petit mal, minor motor, or psychomotor) was significantly benefited by the administration of Mysoline.

TABLE III. RESULTS OF MYSOLINE THERAPY IN THIRTY-NINE PATIENTS WHO HAD BEEN REFRACTORY TO OTHER ANTICONVULSANT DRUGS

TYPE OF SEIZURE	NO. OF PATIENTS	CONTROLLED	MARKEDLY IMPROVED	IMPROVED	FAILURE
Major motor (grand mal)	22	12	4	2	4
Petit mal	3	0	0	0	3
Psychomotor	2	0	0	0	2
Minor motor	3	0	0	0	3
Mixed* (major motor and petit mal)	2	0	1	1	0
Mixed* (major motor and psychomotor)	4	0	2	1	1
Mixed* (major motor and minor motor)	3	0	2	1	0
Total	39	12	9	5	13

These patients received Mysoline in addition to the same dosage of the previous ineffective medication throughout the entire observation period.
*Only the major motor seizures were favorably affected in these cases.

TABLE IV. RESULTS OF MYSOLINE THERAPY IN NINETEEN PATIENTS WHO HAD NOT BEEN TREATED PREVIOUSLY WITH ANY FORM OF ANTICONVULSANT THERAPY

TYPE OF SEIZURE	NO. OF PATIENTS	CONTROLLED	MARKEDLY IMPROVED	IMPROVED	FAILURE
Major motor (grand mal)	6	4	1	0	1
Petit mal	2	0	0	0	2
Psychomotor	2	0	0	0	2
Minor motor	3	0	0	0	3
Mixed* (major motor and petit mal)	2	0	1	1	0
Mixed* (major motor and psychomotor)	2	0	1	1	0
Mixed* (major motor and minor motor)	2	0	0	2	0
Total	19	4	3	4	8

*Only the major motor seizures were favorably affected in these cases.

UNTOWARD REACTIONS

No serious untoward reactions were observed in any of our patients. The character and frequency of those disturbances encountered are shown in Table V.

The most common side reaction of the drug was drowsiness which occurred in nineteen (19 per cent) of the patients. This varied from a mild drowsiness to a severe somnolence. In the majority of the cases the drowsiness appeared within the first few weeks after the onset of Mysoline therapy. In a few instances, it came on after the first few doses were taken. In fourteen patients, the drowsiness disappeared spontaneously

within several weeks after its onset, and treatment with the same dosage of the drug was not interrupted. In the other four cases, the drowsiness was so severe that the patients refused to continue taking the drug.

The next most common side effects were minor disorders of equilibrium: dizziness in seven patients and ataxia in three. In each of these cases the symptoms cleared up spontaneously within one to two weeks, and treatment with the same dosage of the drug was not interrupted.

One patient suffered with a morbilliform rash. This cutaneous reaction appeared ten days after the initial administration of Mysoline. The rash disappeared within ten days after Mysoline was withdrawn. The same dosage of Mysoline was prescribed again to this patient and the rash did not reappear.

Routine urine examinations and blood counts were made on every patient and showed no abnormality at any time.

TABLE V. UNTOWARD REACTIONS MANIFESTED BY THIRTY-THREE OF 100 PATIENTS WHO WERE TREATED WITH MYSOLINE

REACTIONS	NO. OF PATIENTS PRESENTING REACTION	NO. OF PATIENTS IN WHOM DRUG WAS DISCONTINUED BECAUSE OF REACTION
Drowsiness	19	5
Dizziness	7	0
Ataxia	3	0
Skin rash	1	1*
Diplopia	1	0
Nausea and vomiting	2	0

*Mysoline was discontinued when the rash appeared. It was prescribed again after the rash had completely cleared up. The rash did not reappear in association with the second administration of Mysoline.

CONCLUSIONS

Our results with the use of Mysoline in the treatment of epilepsy are in accord with those reported by Handley and Stewart.[2] We also found that Mysoline was an effective anticonvulsant for the control of major motor epilepsy and that it was essentially ineffective against other forms of epilepsy (petit mal, minor motor, and psychomotor). Mysoline completely controlled the seizures in twenty-six (32 per cent) of eighty-one patients who had been refractory to maximum dosages of other anticonvulsant medication.

No serious side reactions were encountered in any of our patients. Drowsiness and minor disturbances of equilibrium were the most frequent untoward reactions observed. These reactions disappeared spontaneously in the majority of the patients within a few weeks after their onset.

SUMMARY

One hundred epileptic patients, mostly children, were treated with Mysoline. The seizures were completely controlled in thirty (30 per cent) of the patients and the number of seizures were markedly reduced in twenty (20 per cent). Mysoline was effective only in major motor epilepsy. No serious side reactions were observed.

The authors wish to thank Dr. Paul H. Pearson for his assistance in the follow-up of some of the patients reported in this study.

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BRONCHIAL ADENOMA

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BRONCHIAL adenoma represents an interesting lesion, diagnostically and therapeutically. We would like to present two cases which emphasize these problems.

The oft-repeated clinical triad of recurring pneumonia, hemoptysis, and the physical findings attendant to bronchial occlusion is well known. It goes without saying that if one waits for recurrent episodes of pneumonia, early diagnosis of this lesion will be frequently missed. It was interesting to note that neither of these two patients (aged 40 years and 4 years) had an appreciable history of recurrent pneumonia.

Frequently, until the patient with bronchial adenoma is x-rayed, the lesion is not suspected. Generally, when a chest film indicates the presence of underlying atelectasis, the correct diagnosis is suspected and the nature of the obstructing lesion is easily investigated by means of laminography, bronchography, and bronchoscopy. Since most of these lesions occur in the larger and main bronchi, biopsy through the bronchoscope is readily obtained and a specific diagnosis is soon forthcoming.

Though the older texts in pathology describe this lesion as essentially benign, many recent articles have emphasized the locally malignant nature, and, on rare occasions, the distantly metastasizing possibility of this lesion. Certainly it is not unusual to find adjacent lymph node involvement on surgical removal. The frequently noted extension of the tumor between the cartilaginous rings into the peribronchial tissue and the tendency toward recurrence of the tumor following bronchoscopic removal of the intraluminal aspect of the tumor are interesting in view of the diversity of opinion as to the anlage of this tumor, some believing they arise from mucosal epithelium, and others, from bronchial buds with mesodermal and endodermal elements.

Microscopy of bronchial adenoma generally reveals a carcinoid or cylindromatous pattern. The carcinoid type is by far the more frequent, occurring nine times more frequently than the cylindromatous type. This differentiation is important since it appears that cylindromatous adenomas are three times as likely to metastasize as adenomas of the carcinoid type.

Articles that have included large series noted that approximately 10 per cent of all bronchial adenomas metastasize. The nature of the metastasis varies from regional lymph node (the most frequent site) to distant organs (liver, lungs, pleura, mediastinum, bone).

It becomes apparent that one must appreciate the pathology and the very potential metastasizing nature of this lesion in order to treat it correctly. Not gainsaying that there may be adequate indication for bronchoscopic removal as the method of therapy, it is

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generally accepted that lobectomy is the treatment of choice, and if that is not feasible because of the situation of the lesion, then pneumonectomy should be performed.

To illustrate the above discussion, we would like to describe two recent cases seen at the Albert Einstein Medical Center, Northern Division. Case 1 (S. A. G.) represents the youngest case of bronchial adenoma seen at this institution and one of the youngest cases described in the literature. Caffey[1] in his text, *Pediatric X-ray Diagnosis*, does not specifically mention this lesion. In the twenty-six cases reported from the University of Toronto by Delarue,[6] the average age was 42 years and the youngest was 21 years.

Fig. 1.

Fig. 2.

Fig. 1 (Case 1).—X-ray revealing atelectasis of left lower lobe.

Fig. 2 (Case 1).—X-ray illustrating partial aeration of left lower lobe following bronchoscopic removal of intraluminal aspect of tumor.

CASE REPORTS

CASE 1.—S. A. G., a white male, aged 4 years, was first seen as an outpatient in order to evaluate the possible presence of a resolving left lower lobe pneumonia as his physician was impressed by the discrepancy in the rather mild clinical picture and definite physical findings. Fig. 1 reveals the classical findings of left lower lobe atelectasis, consisting of homogeneous opacification of the left lower lung field, elevation of the left dome of the diaphragm, and shift of the heart to the left. Because of the patient's age, further roentgen evaluation of these changes by means of laminography and bronchography was not attempted. Bronchoscopy revealed an obstructing polypoid growth in the lumen of the distal portion of the left main bronchus. The bronchoscopist reported a benign growth, polypoid in nature, which could be a tuberculoma. Microscopic examination of the biopsied material revealed an epithelial tumor with pattern of bronchial adenoma.

Following bronchoscopic removal of most of the intraluminal tumor mass, partial aeration of the left lower lobe was obtained (Fig. 2). The child was followed by frequent bronchoscopic examinations and it was gradually noted that the mucosa at this same site became thickened and the lumen narrowed in caliber.

At a seminar discussion, the pathologist emphasized the potentially malignant nature of this lesion. However, in view of the re-establishment

of a patent airway by bronchoscopic manipulation and the concern of the effect of pneumonectomy on the development of the chest cage, surgery was temporarily postponed. As previously noted, gradual occlusion of the left main bronchus recurred and a pneumonectomy was performed (the situation of the lesion did not permit adequate removal by means of a lobectomy).

The pathological specimen of the left lung included a hilar lymph node. Not only had there been extension into the peribronchial area, but replacement of lymphoid structure within the lymph node by adenomatous cells had also occurred. It should be noted that this type of extension into contiguous lymph nodes occurs not infrequently, and does not carry the grave prognosis of lymph node involvement as seen in bronchogenic carcinoma. Two years have passed since pneumonectomy was performed and the patient is clinicallv well at this time.

Case 2.—V. W., a white female, 40 years of age, had a twelve-year history of bronchial asthma. A month previous to her hospital admission, virus pneumonia was diagnosed clinically and this gradually resolved. Three days prior to admission she developed malaise, fever, and cough, the latter being productive of mucus streaked with blood. On admission, since a chest film (Fig. 3) revealed shift of the heart to the left, elevation of the left dome of the diaphragm, and left lower lobe opacification and shrinkage of its volume, the diagnosis of left lower lobe atelectasis was evident.

Though the clinical response to antibiotics was very definite, repeat chest x-rays failed to reveal any appreciable change in the atelectasis of the left lower lobe and laminography, bronchography, and bronchoscopy were in turn performed. Bronchoscopy visualized a large polypoid mass which obstructed the left lower lobe bronchus. Biopsy was obtained and the pathological report was bronchial adenoma, cylindromatous in type.

Following bronchoscopic removal of most of the intraluminal aspect of the tumor, bronchographic examination was performed. This procedure con-

Fig. 3.

Fig. 4.

Fig. 3 (Case 2).—Admission x-ray revealing left lower lobe atelectasis.

Fig. 4 (Case 2).—Left lower lobe bronchography using Xumbradil and demonstrating defect by tumor on inferior wall of left main bronchus.

firmed the bronchoscopic observation as to the situation of the tumor and also permitted planning of the surgical requirements to remove the tumor. A defect was demonstrated on the inferior wall of the left main bronchus opposite the origin of the left upper lobe bronchus (Fig. 4).

These procedures, which permit definite localization, also allow planning as to the type of surgery necesary for adequate removal of the tumor as well as save needless removal of lung tissue. In this case a left lower lobectomy with a sleeve resection of the inferior wall of the distal main bronchus was feasible and was performed.

Case 2 demonstrates the generally accepted diagnostic and therapeutic approach in a case of bronchial adenoma. Unfortunately the age of the patient in Case 1 did not permit all of those diagnostic procedures.

Incidentally, one of us (A. G. B.) has been using water-soluble Xumbradil, Viscous B* (used in Case 2) and has found it fairly satisfactory in about twenty cases of bronchography.

SUMMARY

A brief survey of bronchial adenoma is offered, stressing the roentgenographic, pathologic, and therapeutic features. Two cases have been presented in order to emphasize these points. In addition, Case 1, a male aged 4 years, represents the youngest case of bronchial adenoma seen at this institution as well as one of the youngest reported cases.

*Supplied by courtesy of Astra Pharmaceutical Products, Inc., Worcester, Mass.

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ALLERGENICITY OF MODIFIED AND PROCESSED FOODSTUFFS

IV. Orange: Allergenicity of Orange Studied in Man

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IN A previous study we investigated experimentally in the guinea pig the anaphylactogenic properties of a specially prepared infant orange juice (Bib orange juice*).[1] Our results indicated that it has a low order of anaphylactogenicity as compared with orange seed protein. It was also shown to be devoid of seed protein and peel oil. Within the limits of our experimental data we concluded that this juice was hypoallergenic and nontoxic.

We further noted in the course of our experiments that orange seed protein and juice protein appear to have independent antigenic qualities. Orange peel oil was shown to be nonanaphylactogenic but possessed marked primary toxic properties.

In the present study we undertook the investigation in the human subject of other facets of the allergenicity of this juice.†

EXPERIMENTAL DATA

A serum from a patient highly sensitive to orange (MW) was used for passive transfer by the Prausnitz-Küstner (PK) method in nonallergic children.*

Other modifications of the PK method were also employed, including the dual ingestion passive transfer test described in a previous communication.[2]

The orange seed protein antigen used in these experiments was of high potency.†

I. Twenty recipients (2 to 12 years of age) were passively sensitized with 0.05 c.c. of the human antiorange serum. Twenty-four hours later they were challenged with an intradermal injection of 0.02 c.c. of a 1:100 or 1:1,000 dilution of orange protein at the site of previous sensitization. A positive reaction was obtained in all cases (see Table I), making it evident that the MW serum contained transferrable antibodies to orange seed protein. It was further determined that this serum could be diluted to a titer of 1:80, and remained reactive.

II. (a) Twenty-four children were passively sensitized in two sites on each forearm with MW serum. The following day they were each given 4 ounces of Bib orange juice orally. No reactions ensued.

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*According to the manufacturers this juice is filtered by a special method and contains no orange seed protein or peel oil. It contains 0.045 per cent protein nitrogen. It is especially designed for infants and children. This canned juice was generously supplied to us by the Bib Corporation.

†As we have stated we limited our studies to Bib orange juice because it was signally free from seed protein and peel oil. Time has not yet permitted us to proceed with studies of other forms of orange juice.

*Children at the Sea View Hospital with arrested tuberculosis were used as recipients. They were not suffering from any acute illness at the time of the testing. They ranged in age from 2 to 12 years.

†This protein extract was generously prepared for us by Seymour L. Shapiro, Director of Biological Laboratories of the Arlington Allergy Division of the Hollister-Stier Corporation. The extract used in 1:100 dilution contained 0.075 per cent protein nitrogen.

(b) Two months later ten of the children described in II (a) were again prepared as in the foregoing experiment and each given 8 ounces of Bib juice orally twenty-four hours after passive sensitization. They were observed for two hours and manifested no reactions at the sites of local sensitization.

(c) The mother of patient MW, after being passively sensitized, ingested an even larger amount, 16 ounces, of Bib juice with no evidence of reaction at the sensitized sites. When tested with orange antigen directly at these sensitized sites positive reactions appeared (see Fig. 1).

III. We then injected five of the ten children described in II (b) with 0.04 c.c. of orange antigen, 1:1,000 dilution, intradermally at a remote nonsensitized area. No reactions ensued in the sensitized sites during one and a half hours of observation. A positive reaction would usually occur within a few minutes. Four of these five children were then injected with 0.04 c.c. orange antigen, 1:100 dilution, intramuscularly at a remote nonsensitized area. All four reacted positively at the passively sensitized sites.

IV. Ten children, prepared with MW serum, were treated in the following manner:

(a) At 9:30 A.M., twenty-four hours after sites on the forearm had been passively sensitized, they were given orally 2 ounces of Bib juice mixed with 1 c.c. of a 1:100 dilution of orange seed protein. They were observed for one and a half hours. No reactions ensued.

(b) At 11 A.M. the same children were injected with 0.04 c.c. of orange seed antigen, 1:1,000 dilution, intramuscularly in the left deltoid region (see Table II). A positive, though moderate, reaction (1 cm. erythema) ensued at the sensitized sites in three of the recipients (Cases 3, 5, 9) within

TABLE I. SITE PASSIVELY SENSITIZED WITH MW SERUM INTRADERMALLY AND CHALLENGED TWENTY-FOUR HOURS LATER WITH 0.02 C.C. ORANGE PROTEIN INTRADERMALLY

	1:100 ORANGE PROTEIN		CONTROL SITES	
CASE	ERYTHEMA (CM.)	WHEAL (CM.)	ERYTHEMA (CM.)	WHEAL (CM.)
1.	5.5	3.0	1.0	0
2.	4.5	3.0	0	0
3.	5.5	2.5	0	0
4.	5.5	3.0	1.0	0
5.	3.0	2.0	1.0	0
6.	2.5	1.5	0	0
7.	2.0	1.0	1.0	0
8.	2.0	0.5	0.5	0
9.	5.5	3.0	0.5	0
10.	5.5	3.0	1.0	0.5
11.	3.0	2.5	1.0	0.5
12.	2.0	0.3	1.0	0
	1:1,000 ORANGE PROTEIN		CONTROL SITES	
13.	4.5	2.0	0.2	0
14.	5.0	2.0	0.2	0
15.	4.5	2.5	0.5	0
16.	3.0	1.0	0.2	0
17.	5.5	2.0	0.5	0
18.	3.0	2.0	0.2	0
19.	3.5	2.0	0.2	0
20.	4.5	2.0	0.5	0

TABLE II. REACTIONS IN A SINGLE SITE ON FOREARM WITH ORANGE PROTEIN GIVEN INTRAMUSCULARLY IN THE DELTOID REGION

CASE	0.04 C.C. 1:1,000 ORANGE PROTEIN	0.04 C.C. 1:100 ORANGE PROTEIN
1.	0	0
2.	0	0
3.	1 cm. erythema	1.5 cm. erythema
4.	0	0
5.	1 cm. erythema	1 cm. erythema
6.	0	2.5 cm. erythema
7.	0	1 cm. erythema
8.	0	1.5 cm. erythema
9.	1 cm. erythema	1 cm. wheal, 2.5 cm. erythema
10.	0	0

Fig. 1.—Direct passive transfer test with MW serum. Mother of MW passively sensitized in two sites on each arm with MW serum. Gave negative reactions on ingestion of 16 ounces of Bib orange juice. The reactions were obtained by direct test at sensitized sites with orange seed protein.

one-half hour after injection. The remaining seven children were still negative after two hours' observation.

(c) At 1 P.M. the same ten children were injected with 0.04 c.c. orange seed antigen, 1:100 dilution, intramuscularly in the right deltoid region. Within fifteen to twenty minutes six (Cases 3, 5, 6, 7, 8, 9) had definite reactions at the sites of passive sensitization. Two of the three children (Cases 3 and 9) who had previously reacted with the weaker dilution now reacted more markedly; the third case (Case 5) did not show any enhancement of reaction. Three cases (Cases 6, 7, 8) which did not respond to the 1:1,000 dilution did react with the 1:100 dilution.

V. Another group of ten passively sensitized children was given 8 ounces of Bib juice to which had been added 1 c.c. of orange peel oil. There were no reactions observed at the sites of passive sensitization. However, within a few minutes after this mixture was imbibed all of the children developed an erythematous and irritative reaction which was confined to the perioral region. Several complained of gastric discomfort.

VI. (a) Scratch tests were performed on five normal sites on the backs of each of eleven recipients not previously injected with MW serum. The materials used for the scratch tests were (1) Bib orange juice, (2) Bib juice mixed with orange peel oil in a 1:10,000 dilution, (3) Bib juice with peel oil in a 1:250 dilution, (4) orange seed protein 1:100, and (5) undiluted orange peel oil. No reactions ensued from materials 1, 2, 3, and 4, but erythematous reactions were observed in seven of the cases from the undiluted orange peel oil (5), which were undoubtedly due to primary irritation.

(b) Two patients highly sensitive to orange seed protein (AR and SS) were also tested in the same manner on the back (see Figs. 2 and 3). In the upper row they were tested (reading from left to right) with orange seed, grapefruit seed, and tangerine seed protein. In the lower row (reading from left to right) scratch tests were done with Bib orange juice, supernatant orange peel oil (derived from the oranges used in making the Bib juice), and the centrifuged sediment of the peel oil. In both cases the seed proteins produced typical allergic wheal and erythema reactions. There was no reaction to the Bib juice. The reactions to the oil, however, were a fiery red erythematous area with a vesicular eruption.

VII. These two orange-hypersensitive children were given Bib juice for periods of weeks. In neither instance was this juice the cause of any allergic reaction despite the fact that they portrayed the local reaction to the seed protein and the oil seen in Figs. 2 and 3.

Four additional orange-hypersensitive patients were fed this juice and it was tolerated without allergic reactions.

COMMENT

It seemed quite striking to us that in no instance were we able to show by passive transfer that the protein contained in Bib juice passes through the intestinal wall. Nor could this be demonstrated when orange seed protein or peel was added to the juice, despite the large number of subjects tested and the large amounts ingested. However, when the intestine was by-

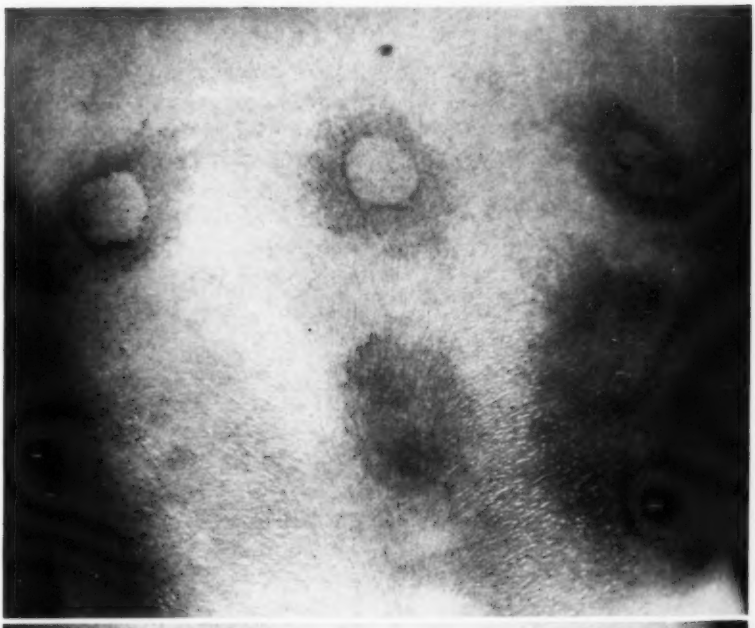

Fig. 2.

Fig. 3

Fig. 2.—Direct skin test on citrus fruit-sensitive patient (AR). *Upper row* (left to right): Orange seed protein; grape fruit seed protein; tangerine seed protein. *Lower row* (left to right): Bib orange juice; supernatant orange peel oil; centrifuged sediment from peel oil.

Fig. 3.—Direct skin test on citrus fruit-sensitive patient (SS). *Upper row* (left to right): orange seed protein; grape fruit seed protein; tangerine seed protein. *Lower row* (left to right): Bib orange juice; supernatant orange peel oil; centrifuged sediment from peel oil.

passed and the orange seed protein was injected parenterally into remote areas, reactions were induced in the sites passively sensitized with MW serum. These studies show, therefore, that Bib juice, though it contains small amounts of orange juice as demonstrated in our previous study,[1] does not contain sufficient protein to traverse the intestinal wall and give rise to allergic reactions at the passively sensitized sites.

These studies again show that orange peel oil does not act as an allergen, but rather as a primary irritant, and thus further corroborate our findings in the lower animal.[1]

In view of the observations that there appear to be independent specificities for orange seed and juice proteins, it is significant that positive reactions were obtained by direct test with the seed protein in highly allergic orange-sensitive cases.

In a previous communication we showed that peanut antigen passes through the intestinal wall with great regularity in the overwhelming majority of nonallergic recipients.[3] We were unable to show such a passage with orange juice and seed protein even when large quantities were given in the considerable number of recipients tested. This is especially interesting in view of the fact that both orange and peanut antibody were present in the same serum (MW). MW was sensitive to both orange and peanut, and the presence of antibodies to both were demonstrated in her serum and this serum was used for both studies. Further, the same recipients were used for passive transfer tests with both substances.

Allergic skin reactions to orange seed protein and circulating antibodies are demonstrable, as in Case MW. Such cases, however, must be rare and the exception rather than the rule. If we seek to explain the reaction to orange seed protein, we may have to conjecture either that some children may chew the seed as well as the pulp, or that in the process of extracting the juice the seeds are broken and the juice thus contaminated with seed protein.

The majority of cases of so-called allergy to orange are probably not true cases of allergy, but rather instances of pseudo- or nonallergic dermal and gastric irritation due to orange peel oil which we have found to be not an allergen but a primary irritant. Indeed, Buffum[4] has shown in a study of asthma in infancy that of eleven cases which reacted clinically to orange, only three gave positive skin reactions to the protein. Hill[5] reported that of five cases that reacted to orange by skin tests, one was correlated with asthma, two with vomiting and hives, and two had no clinical symptoms. Leibowitz and associates[6] demonstrated that when intentional feeding tests were done in eighteen cases with positive skin reactions, only one had a positive clinical response.

The many instances of hand and face dermatitis encountered in the orange industry attest to the nonallergic primary irritative quality of the orange peel oil. Dermatitis occurs in "peelers" who have practically no contact with the juice. The individuals who develop citrus fruit dermatoses seem for the most part to be those who handle and peel these fruits, and they are not sensitive to the juice or pulp. The literature on this aspect is covered by Beerman and co-workers.[7]

In an interesting paper Kesten and Lyons[8] report three cases. One patient, after preparing an orange daily for a number of years, developed an erythematous papular eruption on her neck. It reappeared whenever the oil spray from the peel came in contact with her face or neck. Another patient repeatedly developed a vesicular eruption on her hands only after peeling oranges. A third developed severe dermatitis after handling oranges. The interesting finding in all these cases was the absence of skin reactions to intradermal tests with orange pulp or juice, but a positive patch test with the oil of orange.

These investigators claim to have desensitized the third patient after four months of injections with an extract or orange peel. This may have resulted in an immunity against the toxic principle of the peel oil in much the same way as the immunity to ricin. In so far as we have been unable to demonstrate the presence of an allergen in orange peel oil, we believe that any immunity established must be due to the repeated injection of the toxin.

Joslin and Bradley[9] found that no disturbance of bowel function could be attributed to orange juice in their series of cases. Of 167 normal infants, skin tested by the patch method, 1.8 per cent gave positive reactions to the juice and 5.3 per cent to the orange peel oil. In fourteen cases of infantile eczema, three infants gave positive reactions to orange juice and four to peel oil. They concluded that the maximal reduction of peel oil is important in reducing reactions to orange juice.

When one reviews the studies on the various allergic phenomena, cutaneous or otherwise, [10, 11, 12, 13, 14, 15] 6 to 14 per cent of the cases of allergy were stated to be due to citrus fruits. Alvarez and Hinshaw[15] found that in 6 per cent of 500 patients sensitive to foods "there was a reaction of some sort to orange." One cannot be certain whether these cases were true allergy due to citrus protein or pseudoallergy resulting from contact with the peel oil. It appears, therefore, that what we call allergy to citrus fruit may in truth not be allergy in all instances, but rather an irritation from the peel oil which may produce a dermal reaction from direct contact with the skin or a nonallergic gastric irritation from its ingestion.

CONCLUSIONS

1. Orange juice protein does not appear to traverse the gastrointestinal wall readily even when ingested in large amounts.

2. Only in rare instances does true orange allergy produce such clinical manifestations as urticaria, asthma, or eczema. In these instances the symptoms seem, largely or entirely, to be due to orange seed protein. Though orange seed protein does not readily traverse the wall of the gastrointestinal tract, it was demonstrated to induce allergic reactions when injected parenterally into passively sensitized subjects.

3. Orange peel oil possesses toxic and irritative properties, but is nonallergenic.

4. The local dermatitis and gastrointestinal symptoms, generally attributed to allergy due to orange, are not always allergic in character but rather pseudoallergic dermal and gastrointestinal irritation produced by the primarily toxic orange peel oil.

5. Bib orange juice, which was the only processed product tested in the

present study, is devoid of seed protein and orange peel oil. It is therefore free from allergenic properties found in seed protein and from the nonallergenic irritant found in peel oil. It can safely be ingested by patients who are allergic to seed protein.

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FURTHER EXAMPLES OF ENDOCARDIAL CUSHION DEFECT IN PRODUCTION OF A CARDIAC ANOMALY COMPLEX

A Presentation of Three Cases From Autopsy Reports

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AN ANOMALY complex of the human heart involving (1) patency of the interventricular septum in the region of the roots of the great vessels and (2) transposition or other anomaly of the great vessels, external to the heart, has been recognized for nearly 150 years.[1] We described four cases of this anomaly complex in varying extent in 1944[2] and postulated an embryologic explanation for the association of these particular anomalies.

We assumed that in the early septation of the heart, the ventral endocardial cushion contributed to the union of the interventricular and bulbar septa, just as both cushions at a slightly earlier date provide the union of interventricular and interatrial septa. We assumed further that in the absence or delay of such contribution there would be a failure of these septa to unite with consequent patency of the interventricular septum and that such failure or delay might disturb the septation process of the bulb at an earlier time. Our first assumption was supported by the work of Kramer,[3] which appeared as we went to press. Of work since, the most complete and significant is that of Shaner,[4] who has found and described in the fetal pig, anomalies of the bulb which seem beyond question to be of endocardial cushion origin.

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Since our assumptions of earlier date have been justified by observation, it seems of interest to present three cases which further illustrate this anomaly complex.

CASE REPORT

Case 1 (Acc. No. M6-6).—The patient was a 14-month-old white female, brought to the clinic because of crying and restlessness during the past two days. The child was dead on arrival. She was the youngest of three, having two brothers living and well. The mother had had chicken pox during her pregnancy but could not remember whether her illness had occurred early or late. Birth was attended by a midwife and is presumed to have been normal. Mother recalls that the child at birth looked "queer" and that the midwife said that it was a "blue baby." The child was ill a great deal and did not make significant gains during the first three months of life; since that period, however, she seemed to do reasonably well, and had not been unusually given to illness.

The child appeared to be about the age given, small but moderately well developed and well nourished. The skin was pale but not cyanotic. The heart was found to be greatly enlarged. It was not weighed because it was removed with the lungs en bloc. The striking external feature of the heart was a total absence of pulmonary and aortic roots and in their place a single trunk which emerged from the substance of the heart and terminated in three branches. Superiorly the aorta continued as a branch,

and to the right and left, the pulmonaries. Distal to their origin, the vessels appeared perfectly normal with the exception of a complete absence of a ductus arteriosus or of any remnant which would suggest the position of such structure. The coronary vessels appeared to be normal in position and not remarkable in any way. The coronary sinus was smaller than might be expected on a heart of this size, suggesting that the heart had undergone dilatation and hypertrophy in the brief months of the child's life. Internally was found a complete absence of interatrial and interventricular septa. There was a single atrioventricular opening which was guarded by a four-leaved valve. This valve appeared remarkably normal and functionally competent. The free edges of the leaflets were anchored by chordae tendineae which were related to normal-appearing papillary muscles. Three leaflets were quite large, the fourth being much smaller. Despite this peculiar arrangement, this valve apparently had been sufficient. The myocardium as a whole was in moderately firm condition and deeply ridged. In the root of the single vessel emerging from the ventricle was found a three-leaved semilunar valve in approximately the proper level and having a perfectly normal relation to the coronary arteries at the point of their emergence, right and left. This trunk showed no indication of having ever undergone any degree of septation. The position of the leaflets of the semilunar valve would indicate, certainly, that such was the case. Measurements of this heart taken after a few days' fixation were as follows: circumference just distal to the atrioventricular sulcus, 16.5 cm.; circumference of atrioventricular valve orifice, 6.0 cm.

CASE 2 (Acc. No. M4-8-4).—This is a case of a Negro male stillborn during the eighth month of pregnancy. There is no history on this case nor pertinent information concerning the mother.

A routine post mortem showed a heart externally remarkable for a transposition of the great vessels. The heart, lungs, and thymus were removed en bloc. The pericardium contained a small amount of straw-colored fluid. The heart was normal in size and showed no other anomalies externally. There was a large patent ductus arteriosus.

Internal examination showed a patent foramen ovale and a patency in the interventricular septum just at the root of the great vessels. This opening measured after fixation about 0.75 cm. in diameter. The septum in the region of this fault became so thin as to make measurement of the opening only approximate. The entire myocardium was flabby and of poor tonus. Valves and related structures were normal in appearance.

CASE 3 (Acc. No. M4-11-47).—This patient was a 4-year-old white male who died of bulbar poliomyelitis. The following history is summarized from that obtained at the time of the child's admission to isolation.

The boy had been frail and sickly since birth, making poor weight and growth gains and having numerous respiratory infections, etc. His birth was normal and a sister three years his elder is living and well. The child was delivered by a general practitioner who had taken care of the medical needs of the family for a number of years. Thirty days prior to his death, the mother had brought the child to a larger urban center and consulted an internist upon the recommendation of their family physician. The mother says that the internist told her that the child had a heart murmur and should be hospitalized and studied for possible rheumatic heart disease. Before hospitalization could be arranged for or study instituted, the child contracted polio and died five days after admission.

We were shown the heart in this case because of an unexplained right-sided enlargement. The heart looked entirely normal both internally and externally except for this hypertrophy and a peculiar shallow cone-shaped depression on the left face of the interventricular septum at a point just in-

ferior to the aortic root. Careful probing of this depression showed a canal-like continuity which penetrated the interventricular septum and emerged on the right side of the septum between two ridges of the trabeculae carneae. A vinylite cast of this channel, made after several days' fixation of the specimen, showed its measurements to be as follows: total length, 1.4 cm.; origin on left side, a shallow cone, 0.8 cm. in diameter and 0.2 cm. deep; point of origin or egress on right side, a slit 0.6 cm. in length and without width because of closely adjacent trabeculae. The diameter of the narrowest point in this channel, located just deep to the conelike depression on the left side of the septum, was 0.1 cm.; deep to this constriction the channel was oval in cross section becoming the slitlike terminal portion on the region on the right face of the septum. Direction from left to right was ventrad and craniad with the right opening being as much on the ventral wall as on the septum and at a point just inferior to the smoothing out of the trabeculae for the pulmonary conus arteriosus. Whether this communication from left to right heart was the cause of the hypertrophy of the right side is difficult to say. If it be presumed that this continuity during life had a valve action permitting flow of blood in one direction and not in the opposite, it seems possible that such hypertrophy might be the result. This assumption is offered because there was no other pathology of valves or vessels to account for the hypertrophy.

DISCUSSION

The development of the human heart can be divided conveniently into three periods which are demarked both anatomically and temporally. From the first primordia to the late tubular condition covers the period from the first of the third to the middle of the fourth week of gestation; the period of septation covers from the middle of the fourth to the middle of the seventh weeks; from the close of the seventh week on, the heart, having attained essentially the adult pattern, undergoes changes of growth, position, and spacial rearrangement, chiefly. Thus the period from the fourth to the seventh week is a critical one in cardiogenesis because so many structures first appear and, also, the velocity of the developmental process is at a peak. Of other systems and processes only the central nervous system and the eye are in ascendency of basic development comparable to that of the heart and vascular system, at this same time and one of the most critical periods in central nervous system development, the closing of the neural tube is already past. Of other processes occurring simultaneously, i.e., development of the respiratory system and digestive system, the formation of the face, oral cavity and pharynx, etc., the pace is more gradual and the formation of critical and basic structures extends over a longer period. While the mesonephros is at its ascendency during this time, the development of the definitive kidney and the selection of those portions of the mesonephric system utilized in the final urogenital system does not occur till later. Thus it would seem that the period covering the fourth to the seventh week of gestation is one of more critical significance to cardiac development than to that of any other vital system.

The three cases herewith reported are examples, in varying degree, of failure or retardation of endocardial cushion development early in this critical period. In the first case, endocardial cushions did not appear. Accordingly, if any atrial septation occurred, there was no pillar of tissue inferiorly to act as anchor and what did develop, disappeared. Our knowl-

edge of the dynamics of atrial septation is scant. To what extent endocardial cushion development promotes or influences atrial septation is not clear; in cases of two chambered hearts reported, where there was a total absence of endocardial cushion development, there has been an absence also of anything that could be called atrial septation. In this case, also, the absence of endocardial cushion development left the primitive atrioventricular orifice undivided; this in turn allowed a single column of blood to enter the ventricle and accordingly a single chamber, rather than two chambers with a septum between them, was formed. Finally, the absence of endocardial cushions left the bulb without impetus to ridging and septation and a single aorticopulmonary trunk persisted.

The total absence of a ductus arteriosus in this case is interesting. It will be recalled that the ductus arteriosus serves in the embryonic circulation in shunting the excess blood from the pulmonary system into the systemic system by way of the aorta. In normal fetal life this is necessary because of the smaller demand of the developing lungs for blood as compared to that supplied by the systemic circulation. In this instance the undivided ventricle and undivided aorticopulmonary root served to supply the lungs as all other portions of the body with the blood required; hence there was no excess particularly sent to the lungs that could not be utilized by that developing system. Under these circumstances there was no need for a ductus arteriosus and, at the time the right sixth aortic arch disappeared, the portion of the left sixth arch normally remaining as ductus arteriosus also disappeared. This disappearance was no doubt early and accounts for the fact that there was not even a ligamentous remnant marking the site where the structure might have been.

It would be interesting to know if the mother of this child had the chicken pox during the fourth or early fifth week of her pregnancy. The extensive anomaly suggests a powerfully disruptive force striking at a critical time—in this case the period of the endocardial cushions.

The second case may be interpreted as an example of an early disturbance in endocardial cushion development which subsequently was erased by a more or less normal development. This early deficiency or delay is indicated by two structures; the transposition of the great vessels indicates that the endocardial cushion development was sufficiently delayed to disturb the normal ridging and septation of the bulb. The patency in the far anterior portion of the interventricular septum likewise indicates that although the bulbar septum formed and the interventricular septum formed, the ventral endocardial cushion failed to contribute at the appropriate time that which would have united these two septa and have actually completed septation of the ventricle and bulb. That this early deficiency in development was later compensated is shown by the fact that the normal mitral and tricuspid orifices with their appropriate valves was accomplished. This heart then would seem to be the product of a delay in development, or perhaps one might say, of a faulty timing of the developmental process beginning with the development of the endocardial cushion and ending at what-

ever period the original deficiency was compensated.

The third case here reported is of interest from several viewpoints. The channel which connects the two ventricular cavities passes through that region of the septum and the anterior cardiac walls which is supplied by the ventral cushion and places the specimen in the category we are discussing. Assuming that to be the case, however, a number of interesting problems arise. First is the one as to whether or not this small channel could have accounted for the hypertrophy of the right side. Assuming that it could, then a second assumption would have to be made that this channel had a valvelike action allowing blood, perhaps, to enter from left to right but not return. Careful study of the cast made of this channel and of its points of origin in each ventricle made it seem probable that such valvelike action could or did exist. Yet, of course, it is still in the realms of conjecture since there is no way of proving that such action did take place. If one assumes that this valvelike action did occur, and that the channel allowed blood to pass from the left to the right side, we might account for the clinical history of heart murmur. Since there was no sign of valvular damage it is difficult to account for that murmur, at least anatomically, if this channel and a passage of blood through it did not account for it. If this be assumed to be the case, we approach another matter that is of considerable interest. Only careful examination post mortem would have demonstrated this channel. A more superficial examination of this heart would have left entirely unexplained both its right-sided hypertrophy or any actual anatomic source of the murmur which was described during life. It leads one to wonder if hearts of individuals who have any history or possible suggestion of cardiac or cardiovascular irregularity should not be examined much more carefully than often occurs routinely at autopsy. Here was a case considered probable rheumatic heart disease which apparently rests entirely on a congenital defect.

SUMMARY

Three cases of congenital heart disease manifesting a complex which has been accounted for as a failure or delay in endocardial cushion development have been described anatomically and discussed. This discussion has tended to point to (1) the critical period in development of basic structural anomalies of the heart, (2) the anatomical and embryologic explanation of the three cases presented, and (3) the need of careful post-mortem examination of specimens, particularly in those cases where a history or suggestion of cardiac or cardiovascular irregularity has existed.

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REHABILITATION OF A CHILD WITH NUMEROUS CONGENITAL DEFECTS

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WE ARE reporting this patient for two reasons: her numerous deformities have rarely, if ever, been described in the combination she exhibits, and, second, she demonstrates the possibilities of a carefully planned, comprehensive rehabilitation program.

CASE REPORT

A. N., the youngest of three sisters, was born on Nov. 11, 1940, of young and healthy parents. There is no consanguinity. Pregnancy and delivery were uneventful, with no febrile illnesses, no exposure to x-rays, and no marked dietary abnormalities. Subsequent to the birth of this child, the mother was discovered to be a mild diabetic, but urinalysis during pregnancy was normal.

The patient was hospitalized at the age of 3 weeks for cleft palate, congenital hip dislocations, and intrauterine fractures of both femurs. At 14 months of age a closed reduction of both hips was attempted, and at 18 months she underwent manipulation under anesthesia. At 27 months, an operation was performed for repair of her cleft palate. At this time, she remained in the hospital for a year and a half during which time she was in skeletal traction and in a hip spica.

On admission to the Jewish Sanitarium and Hospital for Chronic Diseases, the child was well-oriented. She spoke a great deal, but so indistinctly that she could be understood only with great difficulty.

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The skin showed two small dollar-sized areas of wrinkled cigarette-paper-like atrophic skin. These two areas involving the most superficial layers were in the left flank and right axilla. In addition, there were symmetrically distributed dimples on the lateral aspects of the buttocks and in the lower axillae. These dimples or hollows seem due to aplasia of the subcutis, with the epiderm appearing normal (Fig. 1). A third type of skin lesion consisted of variously sized hollows, asymmetrically disposed over the trunk and extremities. These lesions were covered by deeply wrinkled scar tissue, rather than by normal skin. The largest and deepest of these areas was on the lower back, over a deformed fifth lumbar vertebra (Figs. 1 and 5).

Her distorted, apelike gait was the next most obvious abnormality. Both lower extremities appeared foreshortened due to marked flexion of both hips and both knees (Fig. 1). Actually, the right thigh was only one inch and the leg one-half inch shorter than the opposite side, but acute flexion of the right knee, fixed at 98 degrees, served to increase the discrepancy, so that the right lower extremity appeared much shorter than the left. The patient compensated for this by holding the right foot in equinus. Both hips had flexion contractures of about 45 degrees, and there was telescoping present on the right side. Further complicating her gait was a bilateral waddle, or side lurch, caused by dislocation of both hips (Fig. 1).

There were old operative incisions at both knees, the sites of previous

osteotomies, and a Smith-Petersen incision over the right hip. The scar tissue was normal in appearance. The upper extremities were normal. Her height was 40 inches; her weight 61½ pounds.

In addition to the congenital and acquired postoperative deformities which so distorted her gait, there were other anomalies of the skeletal system. These included diffuse and erratically distributed osteoporosis (Fig. 2), a cleft palate, synostoses of the metacarpals (Fig. 3), and of the ribs (Fig. 4), irregularities of the terminal phalanges (Fig. 3), deformities of the spine (Fig. 5), sacrum, and pelvis, and distortion of the femurs (Fig. 2).

The head showed a normal contour, without exostoses or deformities. The eyes, ears, nose, and throat were normal. Mouth examination showed a perforation three-quarters of an inch by one-half inch in the soft palate at the junction with the hard palate. The uvula was deviated to the right side. Three teeth were congenitally absent. The upper jaw was mesial to the lower as shown by the relationship of the upper buccal segments to the lower. The upper left canine was in lingual version, and in contact with the upper central incisor. There was loss of vertical dimension which resulted in presentation of two planes of occlusion in the lower jaw. Gingivae were healing. There was a small number of caries.

The neck was supple; no lymph node or thyroid enlargement was felt. The heart, lungs, abdomen, and genitals were normal.

REHABILITATION

The first step in treatment was to determine whether the child's mental development and potentialities warranted a long-term effort toward rehabilitation. Psychological testing showed the child to have an I. Q. of 70 (Wechsler Intelligence Scale for Children) to 76 (Stanford-Binet). She was described as "cooperative, good-natured, resilient; able to form easy relationships with other children and adults; alert, curious and possessed of considerable mental vigor." On the other hand, she was also described as "domineering in her relationship to the nonambulant children; a tendency to resentment and sulkiness when frustrated; general

Fig. 1.—View of patient showing the three types of skin involvement: at the right posterior axillary line, wrinkled atrophic cutis; in the lumbar region, involvement of cutis and subcutis; in the lower right buttock, involvement of the subcutis only. The scar at the right knee is the result of an operation. The picture also shows the foreshortening of both lower extremities, particularly the right, due chiefly to flexion of hips and knees; disproportionate development of trunk and extremities.

Fig. 2.—The deformed sacrum and pelvis with dislocation of both hips and shallow inadequate acetabula; distortion of the femoral heads and necks; osteoporosis of both femoral heads and the right pelvis; sacralization of the lumbar spine; variation in size of the intervertebral spaces.

Fig. 3.—Synostosis of the fourth and fifth metacarpals of both hands; irregularities of the terminal phalanges.

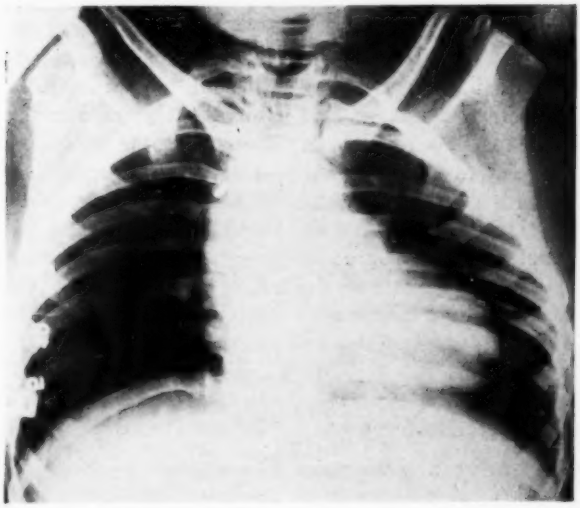


Fig. 4.—Synostosis of second and third left ribs.

Fig. 5.—Flattening of lumbar curve; variation in height of intervertebral discs; decrease in the anteroposterior dimension of the fifth lumbar vertebra and the adjacent part of the fourth.

impoverishment of vocabulary, accentuated by distorted vocalization resulting from her cleft palate; no understanding of abstract concepts and values; incomplete knowledge of family relationships; concept of right and wrong is one of expediency (if you are caught, it is wrong) and not based on ethical concepts; ignorant of essential facts of reproduction." However, the weight of the child's positive qualities seemed to justify a long-term program of rehabilitation.

Speech development was a major consideration. Comprehension and hearing proved to be normal. There was difficulty in directing the air stream through the oral cavity; blowing out of candles was extremely difficult for her. The only true speech sounds present when therapy was initiated were the nasal sounds, *m*, and *n* as in si*ng*.

Work was begun with the *h, w, r, l* sounds, which require proper direction of the air stream rather than maintenance of air pressure in the buccal cavity. Plosive sounds were taught next, starting with the unvoiced sounds *p* and *t*, and proceeding to the voiced sounds *b* and *d*. For these latter sounds, air pressure has to be maintained in the oral cavity for a moment and then expelled through the mouth. She required about three months for easy formation of these sounds. During this same period the foundation was laid for *k* and *g* sounds. The child's tongue was sluggish at the onset of speech and its movements are still not well controlled, so that these sounds, though achieved, still require conscious effort.

Fricatives *f, th* like in thin, *th* like in that, *v, tch* like in chair, *dj* like in jar were completely nasalized; all air was emitted through the nose. A nasal box was an extremely helpful aid in this instance, for by placing one feather in a position where nasal air would blow it away, and a second feather in a position where oral air would blow it away, the child was soon able to distinguish between correct and incorrect air placement.

Sibilants were and still are particularly difficult for her. She has achieved oral emission of air but she still constricts her nostrils and overemphasizes the sounds. Work on *s* combinations and blending, like *st, sk, sm, sn,* has been an arduous task

TABLE I. LENGTH OF TRAINING REQUIRED FOR DEVELOPMENT OF VARIOUS SPEECH SOUNDS

	H*	Y.	F**	L*	STR****
	W*	NG.		DJ	ST****
	M.	K**		SH**	SN****
	B*	G**		+TH**	SM****
	P*	N.		V	CH****
		T*			HW
		D*			-TH
					R*
					S***
					Z
Development in normal children at	3.6	4.6	5.6	6.6	7.6 years of age

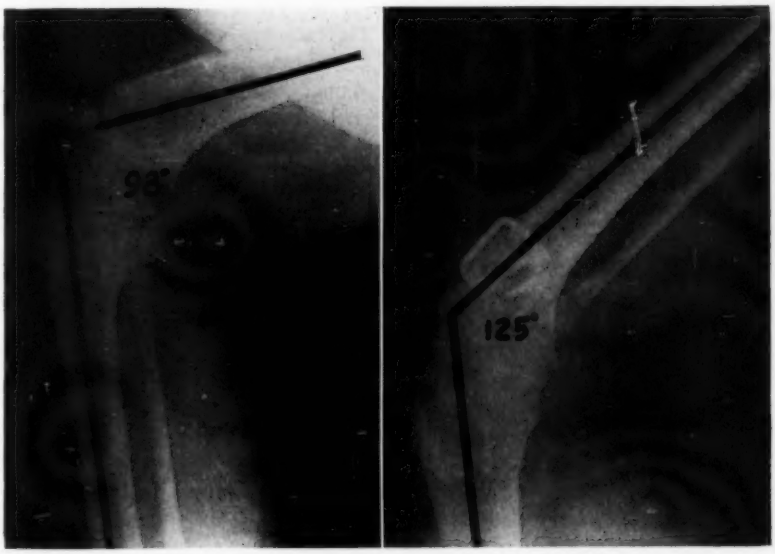
The number of asterisks (*) indicate the number of four-month periods of treatment necessary to attain that sound. The dot (.) indicates that the child could make that sound before treatment began. Sounds not marked are yet to be attained.

+TH means unvoiced *th* sound (thin).

-TH means voiced *th* sound (with).

and *z* and *dz* are still not within her range. Table I summarizes the degree of speech accomplishment to the present.

Further speech improvement depends on completion of her dental and orthodontic work. This includes an obdurator with a bite plate to obtain vertical height and to remove mechanical interference in order to permit bringing the upper left cuspid into its correct labiolingual position. Proper lingual arches and bands are planned and possibly some extractions may be needed in order to harmonize the development of the jaws.



A. *B.*

Fig. 6.—*A*, Roentgenogram showing femur and tibia ankylosed at an angle of 98 degrees. *B*, Eighteen months later: staples in situ, femur and tibia at 125 degrees.

While this orthodontic plan is being completed, a temporary obdurator has been constructed to close off the cleft in the palate and to maintain lateral development. This appliance is made of clear acrylic. It covers the entire palate and is retained by means of clasps around the teeth. This device is expected to practically normalize her speech.

The child's gait with its apelike quality as she lunged forward on her shortened right extremity was exhaustively analyzed. There was a severe flexion deformity of the right knee which appears to have been, at least partly, due to a disturbance at the posterior half of the lower femoral epiphysis, and partly to protracted immobilization in infancy. It was felt that the effective length of the right lower extremity could be increased by straightening the angle at which the knee was ankylosed. Metal staples were inserted anteriorly across the epiphyseal lines of the lower femur and upper tibia at the right knee. By thus restricting the growth of the epiphyseal plates anteriorly and permitting

growth to continue posteriorly, the angle of ankylosis was changed from 98 degrees on admission to 125 degrees after eighteen months (Fig. 6).

Other departments carried on concomitantly. Under the tutelage of the charge nurse, she has become an expert and versatile nurse's assistant. In the Occupational Therapy Department, she is most promising in sewing. The child is thinking about clothes in a serious feminine way and she is devoting much thought to the problem of fitting clothes for the girl with displaced hips. At her request, also, she is being helped with other details of the feminine toilette. It is believed that she should have a future in the area of domestic employment, sewing, child care, or practical nursing.

This eighteen-month period of active rehabilitation has influenced her entire behavior. Public School 401, which is conducted on the fourth floor of the hospital, reports that A. N. has lost much of her aggressiveness and sulkiness. In the school rhythm band, she plays cymbals and does so assiduously, noisily, but with the complete approbation of her fellow pupils. Psychologically, there has been a change from a dominating, aggressive personality, to a helpful girl, motherly toward the less fortunate patients, cooperative, resilient, friendly, and well aware of both her handicaps and potentialities.

The one factor which is essential and which is most difficult to supply in the hospital environment, is motivation. She can and does speak correctly while in the Rehabilitation Department, but motivation is absent on the ward. Lack of motivation, it is believed, accounts for frequent lags in her interests in nursing, sewing, and her other accomplishments. The Social Service Department is searching for a foster home which will perhaps supply the need for a purpose in life. Of course, her rehabilitation will then be maintained on an outpatient basis. When she reaches the age of 14, the Division of Vocational Rehabilitation will take over. We think that by then she will have received a good start toward a self-supporting, reasonably satisfactory life of her own.

DISCUSSION

This child's skin demonstrates three degrees of localized congenital maldevelopment: dysplasia of the ectoderm alone, of the mesoderm alone, and dysplasia of the ectoderm and mesoderm together. Ectodermal dysplasia with widespread anatomical and physiological involvement was first described by a dentist, Guilford.[2] Many others have described the occurrence of skin defects with widespread bone deformities.[3, 4, 5, 6] The combination of congenital deformity of both epidermis and subcutis has also been described[7, 8, 9, 10] but we have seen no reports of patches of apparently pure epidermal or pure subcutis involvement. The entire subject is reviewed by Siemens[11] and by Steiner.[12]

The bone deformities in this patient may be grouped, for convenience, into three categories: (1) impairment and irregularity of epiphyseal development, (2) nondescript congenital anomalies, and (3) osteoporosis.

The dysplasia of the epiphyses is demonstrated by the patient's shortness, her disproportionate growth, and by the irregularity in size of the

intervertebral spaces. Epiphyseal dysplasia is not rare and it manifests itself as chondrodystrophy.[13] Chondrodystrophy in atypical forms has been variously described as Morquio's disease,[14, 15, 16] gargoylism,[17, 18, 19] Ellis-van Creveld syndrome,[20] or calcareous chondrodystrophy.[21] Our case fits into none of these entities.

The nondescript congenital bone defects seen in our patient have all been described previously, but never in combination with the epiphyseal dysplasia and the osteoporosis.

We cannot explain the osteoporosis except on the basis of a congenital hypoplasia of the bone matrix. The patient is certainly not immobile, and endocrine factors have been ruled out by exhaustive clinical and chemical studies.

The rehabilitation program and its continuing success has removed this patient from the category of the rare and curious case to an active and hopeful status. This type of work requires a hospital oriented to the long-term point of view. It requires also a large and specialized staff skilled in many techniques. The coordinating pediatrician must think in terms of the various medical and auxiliary specialties. In addition, he must accept many social, vocational, and economic problems usually left to the parents. It also requires a large and diversified staff, well-trained on a professional and technical level.

SUMMARY

A child with multiple congenital anomalies is presented. A rehabilitation program involving her gait, speech, general education, vocational planning, and psychiatric adjustment is described. This process requires a hospital psychologically and physically equipped for this type of work.

Thanks are due to Dr. Doris Milman who supervised the psychiatric aspect of the program, to Dr. Isaac Karlin who is in charge of the Speech Rehabilitation, and to Mrs. Audrey Smith Hoffnung who carried out the speech program, to Mrs. Frances Schuff in charge of Occupational Therapy, to Mrs. Raya Lister, the Charge Nurse who participated in the attempt to supply motivation and who taught some of her skills to the child, to Miss Roslyn Cooperman of the Social Service Department, and to Mr. Herbert Fischler who took all the photographs.

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BILATERAL EPIDIDYMAL TUBERCULOSIS IN AN INFANT

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ST. LOUIS, MO.

THE rare phenomenon of tuberculosis involving each epididymis in an infant is presented. The incidence of epididymal tuberculosis in infants is infrequent and only a few cases have been found reported in literature. Borthwick[1] in 1945 reported on 402 cases of genitourinary tuberculosis and found 2 or 3 per cent in boys under 5 years of age. None of these had epididymal involvement. Many writers[2, 3, 4] have stressed the rarity of genitourinary tuberculosis in children. Louw[5] in 1948 reported one case of tuberculous epididymitis in a child 19 months of age. Greenberger and Greenberger[6] during an eighteen-year period collected 146 cases where an epididymectomy for tuberculosis was done. The youngest individual in this series was 14 years of age. The greatest number of cases occurred in the age group between 40 and 49 years.

CASE REPORT

E. L., a 2-year-old male, was admitted to Homer G. Phillips Hospital with the finding of bilateral scrotal swelling which had followed an obscure chest lesion. This chest lesion was interpreted by the roentgenologist as an acute inflammatory process, the etiology being undetermined. There was seen in the x-ray of the chest a few clusters of infiltration in the bases of both lung fields. The scrotal swelling progressed to ulceration and drainage followed by periodic healing and breakdown.

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The patient had two previous admissions to the Homer G. Phillips Hospital for this condition without a definite diagnosis. All guinea pig inoculations, smears, and cultures from the scrotal sinuses were reported as negative on these two admissions. He was treated empirically on these two admissions with streptomycin without sustained relief. There was a positive history of tuberculosis contact in the home of the child.

The patient was well developed and well nourished, and in no apparent distress. The pertinent physical findings were as follows: temperature 99.2° F. rectally, pulse rate 104, and blood pressure 110/70. Abdominal palpation revealed no tenderness or masses. The rectal examination was negative.

On examination of the genitals, there was an area of ulceration on the anterosuperior surface of the scrotum approximately 3 to 4 cm. long. The area was nontender and irregular with the surrounding area being indurated. The center of the ulceration was occupied with granulation tissue. The right testicle was uninvolved. The right epididymis was thick and indurated with the vas poorly appreciated. The left scrotum had a draining sinus at the inferior surface. The surrounding skin was indurated. The epididymis was attached to the overlying skin and a draining sinus as seen in Fig. 1.

The laboratory findings included a negative urine for albumin, sugar, and microscopic stain. The red blood count was 4,100,000. The white blood count was 7,300 and the Schilling differential normal. The serology

Fig. 1.—Photograph showing scrotum with draining sinus.

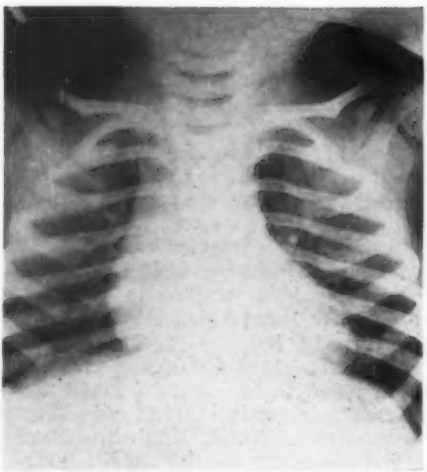


Fig. 2.—X-ray of chest showing no tuberculous lesion.

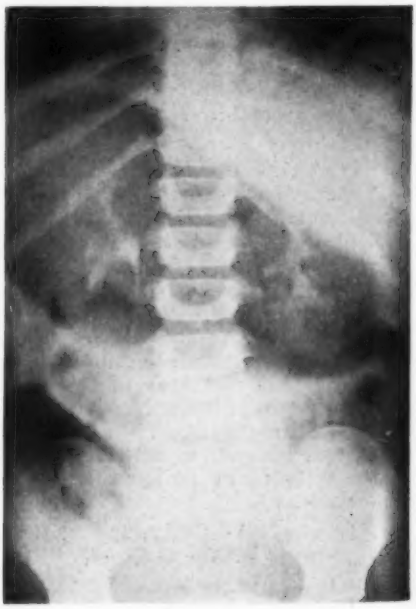


Fig. 3.—Excretory urogram showing each kidney with good function and no deformity.

(Kahn) was negative. Tuberculin was positive. Cultures from the ulcerations on the scrotum grew out *Staphylococcus aureus*. The x-ray of the chest was reported as negative. as seen in Fig. 2.

The excretory urogram was normal. Each kidney had good function with no obstruction and no deformity as seen in Fig. 3.

The management of the case was based on a tentative diagnosis of tuberculosis of the epididymis (bilateral). A two-stage bilateral epididymectomy was performed with a concomitant removal of the sinus tracts

Fig. 4.

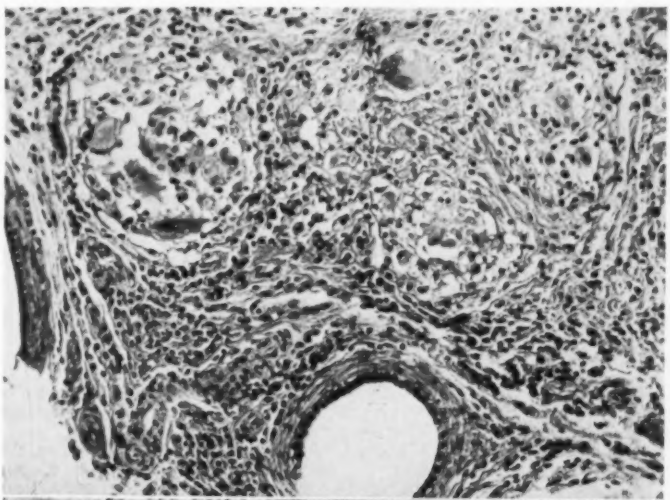
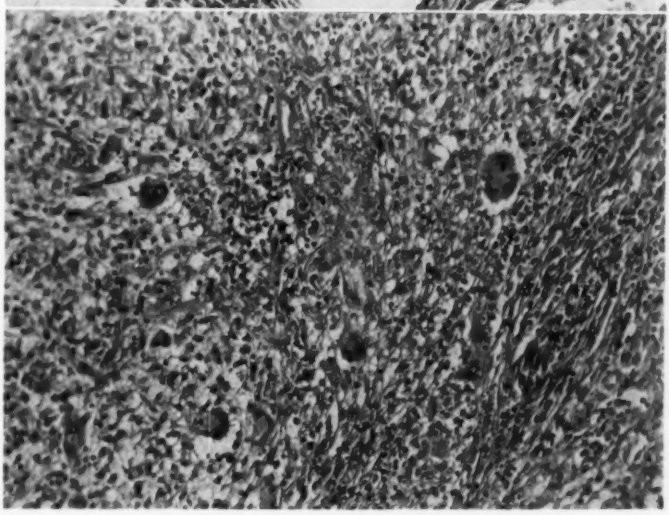


Fig. 5.



Figs. 4 and 5.—Low-power views of epididymitis and draining sinus, showing areas of caseous necrosis with the presence of giant cells.

on April 23, 1951, and May 17, 1951, for the right and left scrotal disease, respectively.

The pathological report of specimens submitted was granuloma tuberculosis, as seen in Figs. 4 and 5. Areas of caseous necrosis are seen with the presence of giant cells. The postoperative course was uneventful. Recent follow-up revealed no further scrotal swelling or sinuses.

COMMENT

Some urologists believe that tuberculous epididymitis is secondary to tuberculosis in the prostate or seminal vesicles. Greenberger and Greenberger[6] after an eighteen-year follow-up study of urogenital tuberculosis concluded that "when tuberculosis is present in the epididymis there are tuberculous lesions in the prostate in most instances, whether they can be demonstrated clinically or not." Medlar and his group[7] reviewed urogenital tuberculosis over a ten-year period at Bellevue Hospital and came to a similar conclusion that "whenever tuberculous epididymal lesions are of microscopic proportions, more than one—and frequently all—of the genital organs are tuberculous." On the other hand, other urologists including Barney,[8] who carefully followed 153 cases and thoroughly reviewed the literature on tuberculous epididymitis, concluded that the epididymis is the primary focus in the majority of cases of genital tuberculosis. In the case presented no clinical evidence existed of tuberculous involvement of the prostate, seminal vesicles, or kidneys. Hematogenous spread to the epididymis from a primary pulmonary tuberculous infection is a probable pathogenesis. The child had a proved tuberculous contact in his home.

In the treatment of tuberculous epididymitis complete removal of the epididymis, prostate, and seminal vesicles has been advocated.[9] With the availability of streptomycin and PAS this appears to be radical therapy, especially in a child.

SUMMARY

A case of bilateral tuberculous epididymitis in a 2-year-old child is presented.

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NEONATAL SYMMETRICAL PEDAL GANGRENE WITH COMPLETE RECESSION

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THE purpose of this paper is to present an extremely rare case of neonatal bilateral gangrene of the feet. The dramatic course of the disease merits attention even though the pathogenesis of the lesion remains an enigma.

H. B. was born on Jan. 19, 1953, and the birth weight was 5 pounds 12 ounces. Dr. E. C. Lidikay, the obstetrician, noted that the cyanosis of the body receded within an average period of time with the exception of the lower extremities. Recession of the cyanosis of the lower extremities was slow but complete with the exception of the feet which twenty-four hours later developed edema with change of the skin color to reddish-purple. Twelve hours later, vesiculation appeared on the dorsal surface of both feet and the ischemia progressed quite rapidly. The femoral, popliteal, dorsalis pedis, and the posterior tibial vessels were definitely palpable. Repeated examination of the infant resulted in negative cardiac findings.

Bacitracin ointment was applied to the feet and heavy bandages were used (at room temperature) as a loose protective covering to ensure that neither constriction nor trauma due to movement of the infant might aggravate the already critical state of ischemia. Improvement was noted beginning on the fourth day, and on the seventh day the feet were entirely normal.

Fig. 1.—Photograph of the feet of H. B. showing discoloration, edema, and vesiculation.

The temperature curve was normal throughout the hospital course and there was no evidence of infection in any part of the body of the infant. The baby weighed 10 pounds 4 ounces at the age of 7 weeks, and progress

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since dismissal from the hospital has been normal in all respects.

Laboratory.—Examinations were made the day following the infant's birth when the disease process was most marked. The hemoglobin was 15.3 grams; the red blood count 5.2 million, and the white blood count 6,600 for each cubic millimeter of blood. The differential count was normal with good platelet distribution.

DISCUSSION

The factors of sepsis, congenital heart disease (emboli from thrombosis of the ductus arteriosus), and trauma were lacking here.

It may be that this infant was born with insufficient development of the arterial supply to the feet and collateral circulation was established.

It emphasized that conservative therapy is the therapy of choice, particularly with present availability of antibiotics.

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SURGICALLY ACQUIRED HYPOTHYROIDISM IN A CHILD WITH COARCTATION OF THE AORTA

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REMOVAL of lingual thyroid tissue results in hypothyroidism if there is no functioning thyroid tissue elsewhere. This situation is infrequently encountered in childhood.[1] Crispell and Parson[2] reported only 5 to 10 per cent of their series of 276 adult patients with lingual thyroid having thyroid tissue in the normal position. The insidious manner in which surgically acquired hypothyroidism was revealed in a child with coarctation of the aorta seems to justify the following report.

CASE REPORT

This 9-year-old white girl had been referred to us in June, 1950, at 7 years of age, because of coarctation of the aorta.

Past History.—The patient was born Jan. 30, 1943, and weighed 5 pounds 2 ounces. Her birth and developmental history was normal. The family history was noncontributory and there was one sibling living and well. A review of systems revealed that she had occasional headaches and leg pains. Her exercise tolerance was apparently normal. In June, 1947, during a physical examination for acute follicular tonsillitis, a tentative diagnosis of coarctation of the aorta was made because the blood pressure determinations were 110/60 in the arms and 90/80 in in the legs. Prior to this time a cardiac condition had not been suspected. An incidental physical finding was a small mass under the tongue. Blood culture, blood counts, and urinalysis were negative. The tonsillitis subsided with penicillin therapy. A tonsillectomy was performed in November, 1949. In January, 1950, the mass under her tongue increased in size and interfered with the swallowing of solid food. The patient was hospitalized in March, 1950, and a round, firm, deeply attached mass was removed from the base of the tongue which measured 2 x 1 x 1 cm. There were no immediate postoperative complications. The pathological report was not available.

Physical Examination.—In June, 1950, she appeared well nourished and well developed, with a short neck and broad shoulders. She weighed 54 pounds and was 47 inches tall. Examination of the eyes revealed normal funduscopic findings. A small amount of mucopus was seen in the oropharynx. There was no chest deformity, and no abnormal pulsations were visible or palpable over the chest wall. The maximal apical impulse was located in the fifth left intercostal space in the midclavicular line, and the cardiac rate was 64 per minute. A very soft systolic murmur was audible in the mitral area and was heard best in the back between the scapulas. Diastole was clear. Blood pressure in both arms was 170 systolic and 120 diastolic. It was not obtainable in the legs. There was no demonstrable atrophy in the legs and the peripheral pulsations were not palpable in the lower extremities. The remainder of the physical examination was thought to be within normal limits.

Laboratory Data.—Fluoroscopy of the chest showed prominence of the ascending portion of the aorta; the aortic knob was not visualized. Barium swallow indicated descent of the aorta on the left. Chest x-ray (posteroanterior, right and left anterior oblique views) confirmed the fluoroscopic findings and there was slight enlargement of the left ventricle. The

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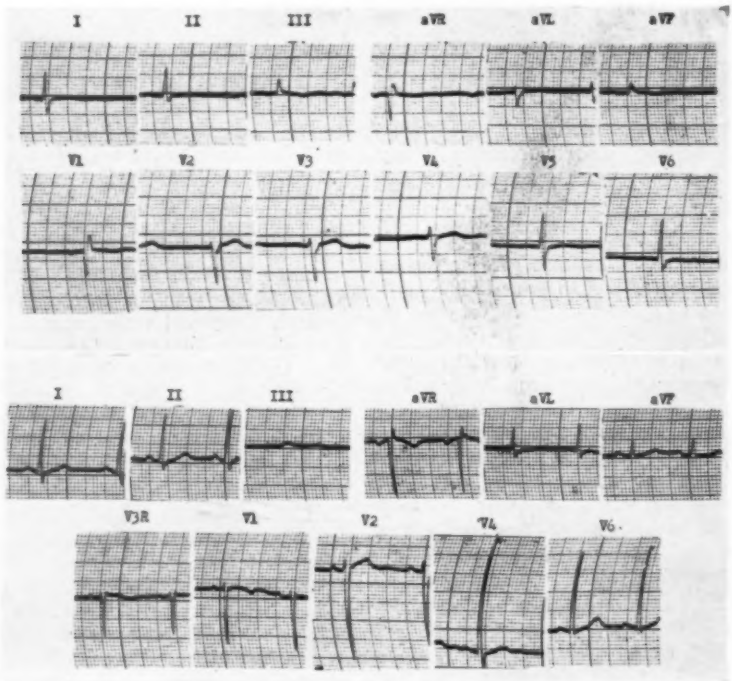
cardiothoracic ratio was 54 per cent and there was no notching of the ribs. X-ray of the cervical spine was normal. The electrocardiogram in June, 1950, showed the following: the cardiac rate was 60 per minute; P-R interval was 0.16 second; QRS interval was 0.08 second. The T waves were flat or of low amplitude in all leads (Fig. 1, *A*). The blood urea nitrogen was 18 mg. per cent and 15 mg. per cent on three follow-up determinations. The red blood count was 4,020,000 with 12 grams of hemoglobin. Urine examination was negative.

Course.—In October, 1950, the patient was examined at another cardiac clinic and the diagnosis of coaretation of the aorta was confirmed. Because of the girl's peculiar appearance (Fig. 2, *A*) an investigation was advised to rule out a possible endocrine disorder. It was felt that surgical correction of the aortic block might have to be undertaken within six months because of the abnormal electrocardiogram which appeared to indicate diffuse myocardial disease and left ventricular strain. In January, 1951, she was further considered from an endocrinological standpoint and it was felt that her general appearance resembled ovarian agenesis. The 17-ketosteroid determination was 5.81 mg. per liter. In six months' time she gained 4½ pounds and developed a deep husky voice, but no secondary sex changes were apparent. Her height was stationary over an eighteen month period. In October, 1951, at

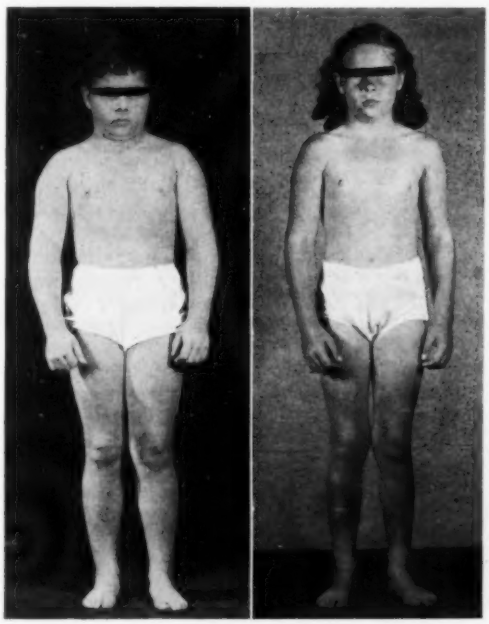
A.



B.

Fig. 1.—*A*, Electrocardiogram before thyroid therapy. *B*, Electrocardiogram after five months of thyroid therapy.

8½ years of age, her skin appeared somewhat coarse and dry and she had a "pasty" appearance. Her body hair, particularly on the extremities, seemed excessive in amount, and the thickset appearance of the neck, shoulders and chest became more pronounced. She appeared pale but her blood count was normal. Her pulse rate was 60 per minute and did not increase with exercise. Because of the possibility of the child's having acquired hypothyroidism, the pathological report of the mass under the tongue was obtained in October, 1951, and was lingual thyroid.



A. *B.*

Fig. 2.—*A*, Before thyroid therapy (October, 1951). *B*, After four months' thyroid therapy, (February, 1952).

X-rays of the long bones showed a skeletal age of 7 years 3 months with a chronological age of 8½ years, which corresponded with the time of removal of the aberrant thyroid tissue and cessation of growth. The patient received ½ grain of thyroid daily, and within two months her resting pulse rate was 75 to 80 per minute and it increased to 96 to 100 per minute following exercise. The color of the patient's skin improved, and she became more alert at school. Her voice changed to a more normal pitch, and in three months she no longer had the heavy-set appearance about the chest and neck (Fig. 2, *B*). The blood serum cholesterol level was 440 mg. per cent following four months of thyroid medication. The basal metabolic rate was –31 per cent prior to treatment and was –9 and +8 after thyroid therapy. The radioactive iodine uptake was 2.81 per cent micrograms.[3] In February, 1952, the patient developed enlarged breasts and pubic hair which would tend to disprove the impression that she might have ovarian agenesis. She was hospitalized on April 21, 1952, for surgical correction of the coarctation of the aorta. Preliminary angiocardiograms were not performed because of the history of a sensitivity reaction to a

test dose of Diodrast made in 1949. At the time of the operation the coaretation site was barely 1 cm. below the origin of the left subcalvian artery and the constriction was approximately 1 cm. in length. The intercostal and internal mammary arteries were thought to be normal in size. A resection of the aorta was decided against at this time because of poorly developed collateral circulation.

DISCUSSION

From the ages of 4 to 9 years this child was under close observation because of a known coaretation of the aorta. Incidentally, at 7 years of age a benign cystic mass was removed from the base of the tongue and, because of its location, the clinical diagnosis of thyroglossal duct cyst was made. Within nine months the patient gradually developed a striking clinical picture which suggested the diagnosis of myxedema, and which resulted in re-evaluation of the pathological study of the mass removed from under her tongue. The presence of a persistently slow pulse rate, the dry, pasty-appearing skin, the short, wide neck, and the marked personality change from alertness to apathy made us suspect the presence of hypothyroidism rather than ovarian agenesis. The pathology report substantiated the clinical impression that the mass was lingual thyroid, and the radioactive iodine uptake determination confirmed a total loss of thyroid function. The abnormalities on the electrocardiograms (Fig. 1, *A* and *B*) suggested a cardiovascular complication, but were proved to be those resulting from hypothyroidism. Schlesinger and Landtman[4] utilized the electrocardiogram in diagnosing the presence of hypothyroidism in twenty-four infants and children in which cretinism or myxedema had been the clinical diagnosis. In ten of their cases, a low-voltage curve with flat or negative T-wave changes was the most common finding. In agreement with their observations, the marked abnormal electrocardiogram changes in our patient disappeared after some weeks of thyroid treatment. Ovarian agenesis is usually associated with a multiplicity of congential defects,[5] and the relatively frequent occurrence of coaretation of the aorta in primary hypoovarianism has been reported by many observers.[6] Although this patient had a "webbedlike" neck, a short, squatty build, and coaretation of the aorta, the appearance of pubescent changes disproved the impression of ovarian agenesis. McGavack[1] related that the presence of lingual thyroid tissue usually passes unnoticed until the time of puberty when the increased functional demand upon the thyroid causes enlargement of the aberrent tissue, but of the three patients with lingual thyroid reported by Goetsch, one was an 8-year-old child in whom the lingual thyroid enlarged following infection and progressed to produce mechanical symptoms similar to our case.[1] A similar report was made by Witte, Mecks, and Trusler on one patient who was also 8 years old.[1]

CONCLUSION

Tissue removed from neck regions should be followed through to pathological diagnosis and, if found to be thyroid, the patient should be followed for the possibility of acquired hypothyroid disease.

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ROENTGENOGRAPHIC DIAGNOSIS OF COARCTATION OF THE AORTA IN A TWO-DAY-OLD INFANT

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CALODNEY and Carson[1] reported a series of twenty-two infants with coarctation of the aorta in fourteen of whom the diagnosis was correctly made prior to autopsy. The diagnosis was established because of the presence of hypertension in the upper extremities and hypotension or absent blood pressure in the legs. In the absence of these findings the diagnosis was not made.

The purpose of this paper is to report a case which demonstrated the actual site of coarctation on the routine posteroanterior roentgenogram in a 2-day-old infant.

CASE REPORT

The patient, a full-term Negro male infant, was born spontaneously to a 35-year-old primipara following an uneventful pregnancy. Ten years before, the mother had an unexplained abortion at three months. Otherwise her past medical history was noncontributory. The father was apparently in good health.

At birth, the infant weighed 7 pounds 5 ounces. Respirations commenced spontaneously immediately after birth. The initial physical examination was felt to be within normal limits. The color and cry were good. Examination of the heart revealed a sinus rhythm with a rate of 120 per minute. P_2 was greater than A_2. No murmurs were audible and the heart was not enlarged to percussion. The lungs were clear and the liver and spleen were not palpable.

The infant was fed sterile water at 12 hours and started on breast feeding at 14 hours. He did well until 48 hours, at which time he was in acute respiratory distress, breathing at a rate of 90 per minute. Minimal subcostal retractions were noted. The skin had a dusky pallid color and the mucous membranes and nail beds were mildly cyanotic. Examination of the heart and abdomen remained within normal limits. The breath sounds at the right base were slightly diminished. The femoral pulsations were faintly palpable. Blood pressures were not obtained.

Roentgenograms of the chest at this time showed cardiac enlargement, increased prominence of the pulmonary vascular markings, and indentation in the descending aorta just above the level of the left pulmonary artery (Fig. 1). The diagnosis of coarctation of the aorta with an associated left-to-right shunt was therefore suggested. The latter diagnosis was considered in addition to the coarctation in view of the increased pulmonary vascular markings.

The dyspnea and cyanosis became progressively more severe despite the use of oxygen, digitalis, Fowler's position, and transfer to the Bloxsom Air-Lock. The liver rapidly enlarged and was palpable at the iliac crest. Reexamination of the heart at 72 hours revealed an apical rate of 110 per minute. The apical first sound was of good quality and P_2 was greater than A_2. A grade IV systolic murmur accompanied by a faint systolic thrill was maximal in the third left intercostal space. The murmur was transmitted widely over the entire chest. Roentgen examination of the chest at this time showed some increase in the cardiac enlargement and a marked increase in the size of the liver.

An electrocardiogram was taken at this time and revealed the following: Normal sinus rhythm was present, at a rate of 108 with normal P waves.

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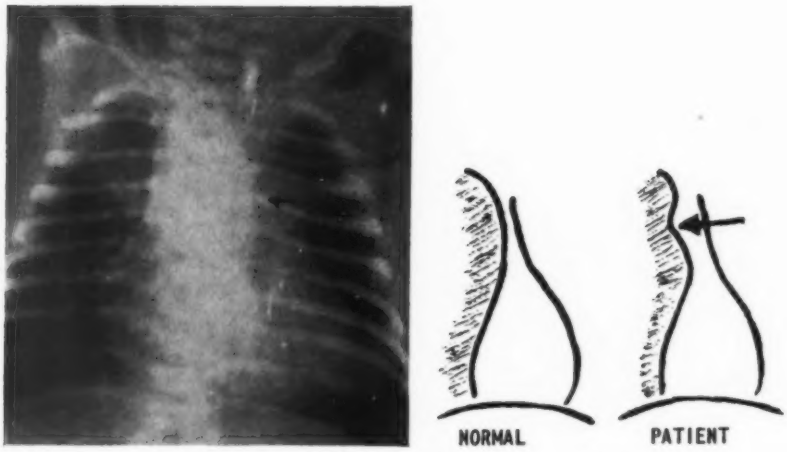

A. *B.*

Fig. 1.—*A*, Roentgenogram demonstrating an indentation in the descending aorta just above the level of the left main pulmonary artery. *B*, Diagram of normal and notched aorta.

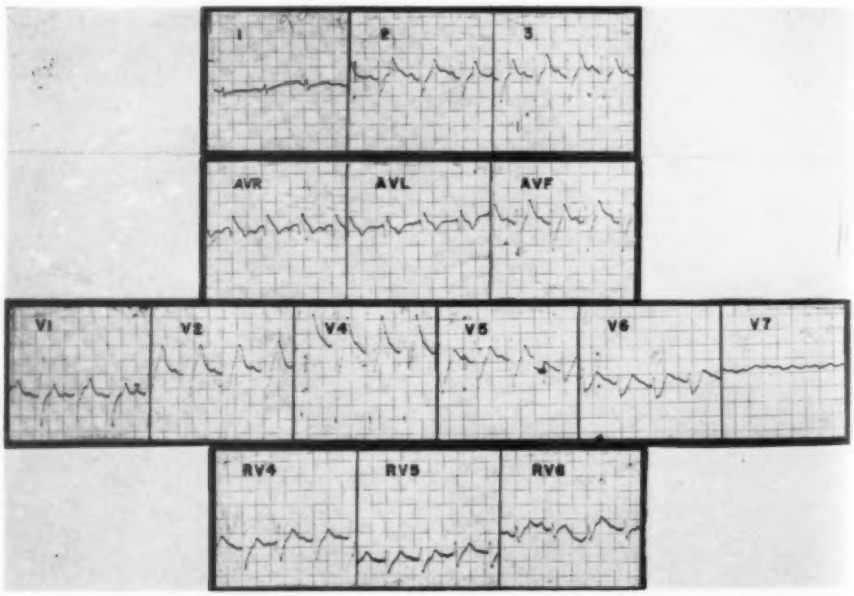

Fig. 2.—Electrocardiogram showing first degree heart block, delayed intraventricular conduction, and evidence of right ventricular hypertrophy.

There were S-T depressions in precordial leads V_5, V_6, RV_5 and unipolar limb lead aV_F. QRS was 0.11 second in duration, P-R interval 0.14 second. The T waves in standard leads II, III, unipolar lead aV_F, and precordial leads V_1 through V_6, and RV_4, RV_5, and RV_6 were upright and tall. The pattern was interpreted as abnormal, showing first degree heart block and delayed intraventricular conduction. Evidence of right ventricular hypertrophy was present but normal for this age (Fig. 2).

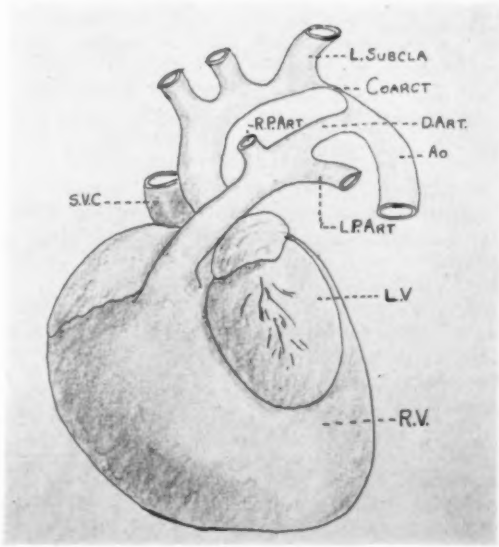

Fig. 3.—Drawing of the heart and great vessels showing the coarctation, patent ductus arteriosus, and small left ventricle lying on the large right ventricle.

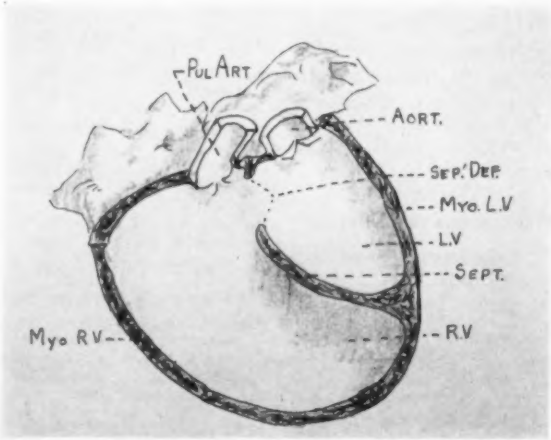

Fig. 4.—Interior of the heart showing the relationship of the right ventricle to the septal defect, the pulmonic valve, and the aortic outflow tract.

Eighty hours after birth the infant became unresponsive, with a fixed stare and a grayish pallor. The dyspnea gave way to slow shallow respirations and in a few minutes to apnea and death.

Autopsy Findings.—The heart weighed 22 grams. In situ there was some dextrorotation so that the pulmonary artery coursed almost directly cephalad and anterior to the ascending aorta. The pulmonary artery and ascending aorta were equal in diameter. The innominate, left common carotid, and subclavian arteries arose normally from a normal calibered aortic arch. At a point immediately beyond the origin of the left subclavian artery the descending portion of the arch became a narrow isthmus with a pin-point lumen for a distance of 0.6 cm. At this point it was joined by a widely patent ductus arteriosus distal to which the aorta resumed its normal lumen.

The heart had four normally developed valves and four chambers. The right ventricle was large and globular. The left was aplastic and rested anteriorly on the right ventricle like an appendage (Fig. 3). There was a high interventricular defect measuring 1 cm. in diameter. The myocardium of both ventricles measured 0.4 cm.

The relationship of the right ventricle to the septal defect, the pulmonic valve and the aortic outflow tract made this, functionally, a trilocular type of heart (Fig. 4). The coaretation was of the infantile type.

DISCUSSION

Most of the roentgen signs of coaretation depend upon the development of a collateral circulation or cardiac enlargement. Thus rib notching, dilatation of the left subclavian and internal mammary arteries and left ventricular hypertrophy are all ancillary indirect signs of coaretation which take time to develop. There is, however, one direct sign which may be present at birth, i.e., actual demonstration of the site of coaretation.

In 1930 Fray[2] called attention to the possibility of visualizing the site of coaretation in the left anterior oblique position. Wolke[3] in 1937 and Bruwer and Pugh[4] in 1952 gave an excellent description of the indentation in the left upper aortic border on the posteroanterior roentgenogram and correctly attributed it to the coaretation.[5] The latter authors state that this finding was present in about one-third of the Mayo Clinic operative cases and was the only roentgen sign of coaretation in 5 per cent of the cases.

SUMMARY

A case of coaretation has been presented in a 2-day-old infant in which the diagnosis was made by the direct visualization of the coareted segment in the roentgenogram.

We are grateful to Dr. Robert Nesbit for his drawings of the heart (Figs. 3 and 4); to Dr. Bernard Mann for his detailed post-mortem examination and analysis of the post-mortem findings; to the other members of the hospital staff for their valuable assistance in the preparation of this paper.

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Medical Progress

HYPOPLASTIC AND APLASTIC ANEMIAS OF INFANCY AND CHILDHOOD: WITH A CONSIDERATION OF THE SYNDROME OF NONHEMOLYTIC ANEMIA OF THE NEWBORN

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IN CLASSIFYING an anemia in patients of any age group, reference is made routinely to established etiologies which include the major items of excessive blood destruction, blood loss, and defective blood formation. These factors, operating singly or conjointly, are identified by appropriate laboratory tests or by supplying specific therapy when a deficiency is suggested. Certain of the anemias, however, are ill-defined, but possess the common hematologic features suggesting impaired red cell formation unrelated to deficiencies of the known antianemic agents or to the presence of space-occupying infiltrations in the bone marrow. This heterogeneous group of anemias includes several well-defined entities and a larger number of hypoplastic states reflecting varying degrees of erythropoietic suppression. In the search for an underlying etiology, the hematologic and clinical data are sifted for clues as to agents which can directly or indirectly inhibit the bone marrow as well as for conditioning influences of prenatal or genetic origin. Occasionally the anemia is recognized as a distinct hematologic entity with conspicuous features, and in others, the pathogenesis of the anemia remains obscure.

These anemias are usually normochromic and normocytic, occasionally hyperchromic and macrocytic with moderate anisocytosis, and are distinguished from other blood dyscrasias by the absence of active blood formation. The absence of enlargement of the lymph nodes, liver, and spleen in the major anemias in this group contributes a feature of diagnostic importance. Their resistance to all forms of antianemia treatment except transfusion accounts for their general designation as refractory anemias.[1] During the course of multiple transfusion therapy, the serum iron already elevated in these anemias is markedly increased, the iron-binding protein becomes completely saturated, resulting in an absent latent iron-binding capacity.[2]

This paper proposes to review some of the more recent concepts of pathogenesis and treatment of the hypoplastic and aplastic anemias in connection with several of the entities belonging to this group. Evidence will be provided to establish pure red-cell anemia as a congenital anomaly on the same basis as other malformations. The syndromes of nonhemolytic anemia of the newborn and of chronic

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hypoplastic anemia of childhood warrant differentiation from the other less well-defined anemias based on depressed erythropoiesis. Emphasis will be given to the early hematologic changes in drug-induced aplastic anemia exemplified by chloramphenicol in the hope of reversing a serious and usually fatal condition. Recent contributions will serve to elucidate puzzling aplastic blood reactions observed during the course of established hemolytic syndromes such as spherocytic and sickle cell anemias. The aregenerative phase and associated anemia noted in isolated instances of erythroblastosis and the inhibiting effects on erythropoiesis of repeated transfusions will also be reviewed.

DEFINITION OF TERMS

Pure Red-Cell, Hypoplastic, and Aplastic Anemias.—For purposes of classification, these anemias can be placed in three general categories. While overlapping obviously occurs, members of each group, nevertheless, present certain well-defined criteria which permit consideration of their individual pathogenesis. Pure red-cell anemia is a chronic aregenerative anemia, in which the failure of the bone marrow is confined to erythropoiesis without simultaneous depression of the granulocytes, platelets, or their precursors. Hypoplastic anemia, with which pure red-cell anemia has been heretofore grouped, has in recent years included assorted conditions marked by impairment of red cell formation with varying degrees of involvement of granulocytes and platelets. In aplastic anemia, on the other hand, the three principal cellular elements in the bone marrow are depressed, resulting in a pancytopenia.

There is in addition a large intermediate group difficult to classify, which ranges in severity from pure red-cell anemia to fatal progressive aplastic anemia, in which the cellular components of the bone marrow cannot be accurately correlated with the peripheral blood picture. Hypoplastic anemia, to which these obscure cases are generally assigned, refers to varying degrees of lessened hematopoietic activity which are frequently reversed by treatment, undergo spontaneous remissions, or represent a stage in the development of aplastic anemia.

Splenic Panhematopenia.—This condition included by Abt[3] in his recent review of aplastic anemias in childhood has been omitted from the classification proposed in this paper (Table I), because in the former the spleen rather than the bone marrow is predominantly implicated in pathogenesis of the peripheral blood picture. In the primary and secondary forms, the bone marrow contains its full quota of each of the cellular elements, or it may be hyperplastic, differing in this respect from aplastic anemia in which depression of the bone marrow represents a constant feature. In children, except for isolated areas of activity, the bone marrow usually reveals complete aplasia. Pancytopenia in splenic hematopenia has been explained on the basis of an abnormally functioning and usually enlarging spleen in which either sequestration or destruction of the formed elements occurs[4] or which exerts inhibitory effects upon a normally functioning or hyperactive bone marrow.[5]

Factors in Appraisal of the Blood Picture.—The problem of accurate designation is exemplified by the report of Cathie[6] who described five chil-

dren with congenital hypoplastic anemia approximating "pure red-cell anemia" under the heading of "erythrogenesis imperfecta" in which serial bone marrow examinations have shown a variation between erythroid hypoplasia and hyperplasia. Estren and Dameshek[7] also have described as hypoplastic anemia, a familial disorder with hypoplasia of the bone marrow and pancytopenia. The absence of multiple congenital anomalies, however, differentiates it from Fanconi's syndrome[8] which is classified as aplastic anemia.

fetal life, to account for defects in hematopoiesis sometimes linked with well-defined structural abnormalities.

PURE RED-CELL ANEMIA (CHRONIC CONGENITAL AREGENERATIVE ANEMIA)

Description and Clinical Course.—The term "pure red-cell anemia" originally applied by Lescher and Hubble[9] to isolated aplasia of the bone marrow in respect to erythropoiesis has also been designated as congenital aregenerative anemia by Vogel, Erf, and Rosenthal,[10] and essential erythroblastopenia by Hansen.[11] It has been

TABLE I. HYPOPLASTIC AND APLASTIC ANEMIAS OF INFANCY AND CHILDHOOD

- I. Pure red-cell anemia (chronic congenital aregenerative anemia)
- II. Hypoplastic anemia
  - A. Subacute and transient
    - 1. Nonhemolytic anemia of the newborn
    - 2. Erythroblastopenia and aplastic crisis during:
      - a. Infectious, toxic and allergic states (Gasser)
      - b. Hemolytic syndromes: spherocytic and sickle cell anemia, etc.
    - 3. Depression of erythropoiesis
      - a. Following prolonged blood destruction: erythroblastosis
      - b. Repeated blood transfusions
  - B. Chronic
    - 1. Familial (Estren and Dameshek)
    - 2. Nonfamilial
      - a. Idiopathic
      - b. Secondary: Chemicals, chemotherapeutic agents, infection, radiation, radioactive substances, bone marrow encroachment, etc.
- III. Aplastic anemia
  - A. Idiopathic or primary
    - 1. Acute
    - 2. Chronic
      - a. With multiple congenital anomalies (Fanconi)
      - b. Without associated anomalies
  - B. Symptomatic or secondary: as in chronic hypoplastic anemia

Because of the shift in normal hematologic values extending from birth to childhood, a particular blood picture must be measured against the background of the contemporary hematic state. The evaluation of the normal blood picture should also include an investigation of genetic factors and a search for possible environmental disturbances extending into

separated from the group of hypoplastic anemias because the failure of hematopoiesis is restricted entirely to the erythrocytes without simultaneous impairment of leukocyte or platelet production. The earlier descriptions of this disorder by Josephs[12] and by Diamond and Blackfan[13] emphasized the feature of chronic progressive anemia and correlated with it a failure of

erythropoiesis without an equivalent depression of the white blood cells or platelets. The disease has an insidious onset with progressive pallor and anemia which is usually detected in the latter part of the neonatal period or at some later month in the first year. Exceptionally, similar cases with a retarded onset have been reported, such as one by Hansen[11] in a child 6 years of age, and by Moeschlin and Rohr[14] in an adult of 20 years. The latter patient suffering with bouts of polyarthritis revealed for three years isolated absence of erythroblasts from the bone marrow with anemia controlled by frequent transfusions. This condition termed "erythroblastophtisis" may represent a more chronic form of the transitory acute erythroblastopenia associated with toxic, infectious, or allergic etiologies described by Gasser.[15]

In the typical case of pure red-cell anemia, the disease is fully established in early infancy with a blood picture consisting solely of a severe normochromic and normocytic anemia, and a pathognomonic bone marrow characterized by the presence of an occasional normoblast or other red cell progenitor without quantitative alteration of the other marrow elements. There is no evidence of increased hemolysis, the white blood cells and platelets are normal in number and the granulocytes are not reduced. The liver and spleen are not enlarged until after transfusions have been given for prolonged periods. The effect of the long-standing administration of blood is reflected in hemosiderotic deposits with moderate increase in size of these organs and darkening of the skin. In this condition, also, the bone marrow frequently contains varying numbers of primitive cells termed hematogones.[16, 17] Usually smaller than the ordinary lymphocytes, they resemble them closely in size and morphology. They possess a dense homogeneous matlike nucleus and a narrow rim of nongranular basophilic cytoplasm which is usually entirely absent in lymphocytes. These primordial cells possibly represent progenitors of the erythrocytic series. In one instance following the use of cortisone, they were replaced by small numbers of normoblasts.

Treatment.—Patients with "pure red-cell anemia" survive long periods, provided repeated transfusions are administered to maintain normal blood levels. Cases have been reported with a spontaneous recovery at subnormal blood levels.[18] Splenectomy has been occasionally effective in arresting the anemia, but definitive criteria for recommending this procedure have yet to be established. The encouraging results reported with corticotropin in several cases of refractory anemia[19] prompted the trial of this substance in the two cases to be described. Neither patient showed any response in the bone marrow or peripheral blood with trials of ACTH and cortisone. Gasser,[20] however, recently reported a marked return of erythropoiesis in the bone marrow with improvement in the anemia following the use of cortisone in an infant in whom a condition closely resembling "pure red-cell anemia" followed measles. The extraordinary bone marrow response with the appearance of normal numbers of nucleated red cells and peripheral reticulocytes occasionally observed with the use of ACTH and cortisone may categorize a group that is marked for eventual recovery with and without

splenectomy. The favorable results attained with removal of this organ in reported cases may represent the elimination of an inhibiting force depressing erythropoiesis as well as an excessive hemolytic influence resulting from structural changes due to frequent transfusions.

In a comparable group of cases designated as stationary hypoplastic anemia, Palmen and Vahlquist[18] noted varying degrees of leukopenia with a normal differential count. While this was not observed in the two cases described in this paper, it will nevertheless be noted that both (Tables II and III) reveal a decrease in cellularity of the bone marrow as indicated by the progressive decline in the total count of nucleated cells. It is difficult to determine whether this change represents hypoplasia extending to other cellular elements inherent in the disease or whether this contraction of hematopoietic tissue results from the depressing effects of frequent transfusions to be discussed in a later section of this paper.

In emphasizing the functional uniformity of the bone marrow, Nordenson[21] notes that changes in any one of the three component systems of blood formation do not long remain isolated, but eventually affect the others. The paucity of cases of pure red-cell anemia in any one clinic has precluded definite statements as to their hematologic and clinical course. It is hoped that comprehensive studies based on long-term follow-up collected from many clinics will eventually resolve these difficulties and provide a basis for rational therapy.

Pure Red-Cell and Related Hypoplastic Anemias as Examples of Congenital Hematopoietic Anomalies.—It will be noted in Table I that hypoplastic anemia embraces a number of syndromes, ranging from cases with a normal bone marrow to intermediate conditions in which the three blood elements in the marrow are depressed in varying degrees. Pure red-cell anemia, from which it has been separated, lends itself to scrutiny as a hematopoietic defect resulting from fetal injury. Two cases will be cited briefly, as supportive evidence for this thesis.

CASE 1.—A. K. (Table II), a 6-year-old boy, was previously reported in another communication[22] when he was 17 months old. The onset of the anemia was dated to the newborn period, with the clinical and hematologic features of a mild type of erythroblastosis. The mother's blood group was O, Rh positive, and the infant and father, A, Rh positive. The anti-A serum titer in the mother reached a maximum of 1:128,000. Repeated examinations of the bone marrow have consistently revealed an absence of erythropoiesis without alteration in the granulocyte and platelet elements (Table II). It was postulated that prolonged depression in red-cell production resulted from an antibody directed solely against red cells and red cell precursors in fetal life. This selective developmental defect in this instance probably originated during the first trimester of fetal life, when A and B factors are developed. It was emphasized that the explanation for the mechanism of the anemia in this case was not expected to account for the pathogenesis of all instances of this entity, and may have operated only in this patient.

The case for anomalous development of erythropoiesis in the fetus is exemplified by another child in whom a unilateral cystic hypoplastic kidney coexisted with pure red-cell anemia.

CASE 2.—L. B. (Table III), a 5½-year-old girl, was observed to be pale from birth. Blood examinations at

TABLE II. REPRESENTATIVE HEMATOLOGIC DATA IN CASE A. K., PURE RED-CELL ANEMIA
Born Dec. 28, 1946

BONE MARROW ASPIRATION	MAR. 11, 1947	JAN. 31, 1951	APRIL 11, 1952
Total nucleated cell count per cu. mm.	132,500	120,000	40,000
Myeloblasts	0	0	2
Myelocytes	12.5	15	14
Metamyelocytes	7.5	0	2
Polymorphonuclears: nonsegmented	30.5	18	21
segmented	9.0	18	11
Eosinophils	0	3	0
Lymphocytes	39.5	44	50
Nucleated red cells	1.0	1	0
Megakaryocytes: Present in all smears			

PERIPHERAL BLOOD COUNTS	MAR. 14, 1947	JAN. 15, 1951	APRIL 18, 1952
Hemoglobin Gm. %	8.9	8.0	7.4
Red blood cells per cu. mm.	------	3,700,000	2,500,000
Platelets per cu. mm.	390,000	adequate	200,000
White blood cells per cu. mm.	19,450	5,300	9,450
Polymorphonuclears	35.5	48	40
Lymphocytes	52.0	46	55

Reticulocytes: Absent or below 1%.
ACTH: 40 to 80 mg. daily Jan. 17 to Feb. 5, 1951; range of nucleated cells in marrow during this period 1 to 2%.
Range of hemoglobin: At times 6 to 6.7 Gm. %; usually elevated by frequent transfusions.
Jan. 31, 1951: Serum iron—393 μg per 100 c.c.; latent iron binding capacity—0.

TABLE III. REPRESENTATIVE HEMATOLOGIC DATA IN CASE L. B., PURE RED-CELL ANEMIA ASSOCIATED WITH CYSTIC KIDNEY*
Born Sept. 11, 1947

BONE MARROW ASPIRATIONS	OCT. 31, 1947	APRIL 28, 1949	SEPT. 11, 1951	MAY. 29, 1953
Total nucleated cell count per cu. mm.	82,600	59,000	22,250	12,150
Myeloblasts	2	0	0.5	0
Myelocytes	16	22	4.5	8
Metamyelocytes	7.5	7	7.25	0
Polymorphonuclears: nonsegmented	9	12	0	10
segmented	9.5	9	7.0	19
Lymphocytes	41	50	79.75	50
Nucleated red cells	0	0	0.5	0
Hematogones	15	0	0	10
Eosinophils	0	0	0.5	3

PERIPHERAL BLOOD COUNTS	OCT. 29, 1947	DEC. 21, 1948	OCT. 9,† 1951	MAY 29, 1953
Hemoglobin Gm. %	7.0	4.5	5.6	8.3
Red blood cells per cu. mm.	2,400,000	1,800,000	2,150,000	2,450,000
Platelets per cu. mm.	300,000	adequate	200,000	130,000
White blood cells per cu. mm.	12,100	19,700	5,000	6,250
Polymorphonuclears	57	52	43.5	41
Lymphocytes	42	44	48.5	58

Oct. 2, 1951: Serum iron—280 μg per 100 c.c.; latent iron binding capacity—0.
Megakaryocytes: Present in all smears.

*Nephrectomy: Nov. 18, 1948.
†After course of cortisone therapy, 100 mg. daily, Sept. 11 to Oct. 9, 1951.

approximately 1 month of age revealed a hemoglobin of 37 per cent and a red count of 2,340,000 per cubic millimeter. The child was admitted to The New York Hospital at this time for evaluation of a kidney mass noted soon after birth, and the anemia. Repeated bone marrow examinations showed the depression of erythropoiesis with a normal number of granulocytic and platelet elements. With clinical and laboratory examinations pointing to abnormality of the left kidney, a nephrectomy was performed at 2 months of age, and a small cystic kidney was removed. The pathologic diagnosis was congenital dysplasia of the kidney. The total count of nucleated cells in the marrow has shown moderate fluctuations, but the consistent finding has been a depression of hematopoiesis and peripheral anemia without thrombocytopenia or granulocytopenia. This child has from birth received periodic blood transfusions.

In this instance, removal of the cystic and hypoplastic kidney did not alter the course of the anemia and the bone marrow revealed persistence of erythropoietic depression (Table III). The causation of cysts of the kidney has not been definitely established, but the current concepts of their pathogenesis have been reviewed in a previous paper.[23] The association of polycystic kidneys with more widespread derangements in the same person such as cysts in other organs has been frequently observed.

It is noteworthy that the important developmental changes in hematopoiesis and in the urinary system occur within the first two months of embryonic growth. Although the causative agent is unknown, it may be postulated that the same disturbing factor may have engendered the simultaneous injury in both organs at critical periods of their development, resulting in the combined production of a cystic hypoplastic kidney and a defect in red cell synthesis.

Normal Embryonic Development and Experimental Production of Defects.—The experimental production of developmental defects in vitamin-deficient rats by Warkany[24, 25] and those resulting from anoxia in the pregnant mouse described by Ingals, Curley, and Prindle[26] have prompted a consideration of multiple anomalies in the newborn infants in the direction of maternal-fetal relationships. In a recent review, Bass[27] presented a growing body of evidence in support of the association of a variety of disease states in the mother and the occurrence of abnormalities in the offspring. The greater number of congenital defects await explanation, and probably depend on insidious influences affecting the developing embryo at critical periods. Stockard's[28] fundamental investigations are pertinent in connection with the origin of groups of divergent anomalies in human beings. He concluded that the type of deformity depends upon nonspecific noxious influences operating at "developmental moments" corresponding to periods when organs are in their most rapidly proliferating condition. According to current interpretation, coexisting anomalies or synchronisms represent deviations from orderly development, probably dating from the fifth to the eighth week of embryonic life, and induced by a known infection, such as rubella, or other as yet unidentified agents or states, acting upon the pregnant woman and the placenta.

Blood Dyscrasias in Relation to Fetal Conditioning.—The extension of this hypothesis to embrace blood dyscrasias relating them to fetal conditioning can be further documented by isolated instances recorded in the literature. No exhaustive survey has been made in the latter group, but a

few pertinent examples have been chosen. In an infant now 2 years of age, anemia was noted at 18 days, with a hemoglobin value of 5.6 grams per cent, and a red count of 1,840,000. The mother's blood group was B, Rh positive, and the infant's, group A, Rh positive. The mother's titer for A was 1:400, and the infant's Coombs test was negative. At 9 weeks, the bone marrow was normally cellular, except for the presence of only 4 per cent nucleated red cells. Except for sporadic elevations to a maximum of 17 per cent, the nucleated cells have usually fluctuated from 3.5 to 7 per cent. These levels, though markedly diminished, suggest hypoplastic rather than pure red-cell anemia in which normoblasts are either absent or appear in minimal numbers. Anemia, however, has persisted and periodic transfusions have been necessary. The platelets and granulocytes have remained normal. In the course of the first year, hydrocephalus and hypogenitalism became apparent. The case may possibly represent the suppressive effect on fetal erythropoiesis of an incompatible pregnancy with reference to the "A" blood factor, despite the low anti-A titer. More likely, the anemia and the associated abnormalities indicate acquired malformations of prenatal origin of unknown etiology.

There is also suggestive evidence that certain of the blood dyscrasias which are not observed until childhood represent congenital developmental defects within hematopoietic sites in the embryo, affecting one or more cellular elements. It is difficult to designate a definite time during gestation in which interference with erythropoiesis takes place. Accepting the principle that for all organs injury is most likely during the stage of active differentiation, the vulnerable period for erythropoiesis would extend from the sixth to the twelfth week, when the liver, spleen, and bone marrow are simultaneously involved in the proliferation of erythroblasts.[29, 30]

The "Fanconi Syndrome" and Related Disorders.—Benjamin[31] described three children in whom skeletal and mental retardation, hydrocephalus, and genital hypoplasia occurred in varying degree in association with severe refractory anemia. Esser[32] reported a similar case in a young child with congenital anemia and a number of malformations. The defect restricted to the red cells could be traced in the bone marrow to a diminution in normoblasts and an increase in reticulum cells. In their report on stationary hypoplastic anemia, Palmen and Vahlquist[18] described a child who showed, in addition to the anemia, congenital malformation of the heart, small stature, and mental retardation, and referred to this combination in other reported cases. The best known group of congenital malformations in which anemia constitutes an outstanding symptom is represented by the "Fanconi syndrome."[8] This condition includes the rare association of aplastic anemia with a number of congenital abnormalities, chiefly pigmentation of the skin, testicular hypoplasia, and skeletal abnormalities, although other less common defects have been observed. Originally reported by Fanconi as occurring in three siblings, sporadic as well as familial cases have since been reported. An isolated case observed at The New York Hospital

was that of a boy of 4 years with a congenital absence of the left thumb and radius, whose blood showed pancytopenia and hypoplastic marrow. Similar single instances in a family have been described by others, more recently by Estren, Suess, and Dameshek,[33] Silvers, Blair, and Kempe,[34] Crisalli and Sansone,[35] Demirag,[36] and Cassimos and Zannos.[37] More recent reference to the occurrence of several siblings in one family has been made in the reports of Levy[38] and of Reinhold, Neumark, Lightwood, and Carter.[39]

In designating pure red-cell anemia and related conditions as congenital anomalies, the overlapping influence of heredity and environment are brought into consideration. According to Warkany[24] the repeated appearance of defects in a family indicates the influence of a dominant or recessive inheritance of abnormal genes, or of the repeated exposure of the developing embryo to the same adverse environmental factors. A purely genetic mechanism without environmental intervention accounts for the transmission of certain blood disorders, notably sickle cell anemia, hemolytic jaundice, Mediterranean anemia, hemophilia, and for the transmission of diverse fetal erythrocyte antigens leading to erythroblastosis.

There is, in addition, suggestive evidence that either environmental or genetic factors operating singly or together are responsible for bone marrow hypoplasia with peripheral blood disturbances. The familial aspects of the Fanconi syndrome and of related blood disorders may be attributed to the interaction of environmental and genetic factors. Pure red-cell anemia has been observed in two children in one family,[40, 41] and in another family observed at The New York Hospital, fatal idiopathic aplastic anemia occurred in first cousins each 7 years of age, and hypoplastic anemia in a sister of one of them. Estren and Dameshek[7] reported eight cases of anemia in two families in which several siblings of each had pancytopenia, a hypoplastic marrow, but no other developmental malformations as in the fully established Fanconi's syndrome. Similar familial and sporadic examples of refractory anemia with and without congenital defects are cited in the papers by Dacie and Gilpin.[42] They contributed two cases of their own in brothers with this type of anemia, one with a renal developmental abnormality, the other free from other defects. There was a history in this family that a cousin had died of aplastic anemia. Reinhold, Neumark, Lightwood and Carter[39] observed two siblings in one family with hypoplasia of the bone marrow and other congenital abnormalities and three siblings with congenital abnormalities but without blood changes. Kunz[43] described two siblings, both with multiple congenital anomalies, in one of whom hematologic symptoms were present. The onset of anemia between 18 months and 2½ years in the latter case is earlier than usual in Fanconi's syndrome. This blood dyscrasia and its variations with or without coexisting constitutional disturbances occur almost exclusively in children. The rare counterpart in adults was reported by Rohr[44] in two brothers, 20 and 24 years of age, with hemorrhagic manifestations, bone pains, and pancytopenia in both, and

with moderate infantilism in the younger. The familial occurrence of congenital deformities in siblings with and without anemia provides additional support for the intrauterine origin of the hematopoietic disturbances analogous to other somatic derangements.

It is noteworthy that the reports bearing on the relationship of congenital malformation to maternal rubella[45] list no defects involving either the hematopoietic system alone, or in conjunction with other congenital anomalies. The evidence, however, that has been presented demonstrating injury to single or multiple cell types in the marrow in combination with other well-defined somatic defects supports the hypothesis of embryonic hematopoietic disturbances as a causative factor in blood dyscrasias. The relative infrequency with which these disorders can be unequivocally traced to a defect originating in the embryo occurring alone or in association with other malformations may possibly be explained by the improbability of survival with serious disturbances of erythropoiesis. The infrequent association of severe types of hematologic disorders with other congenital malformations suggests the relative resistance of hematopoietic tissues in comparison with the vulnerability of other systems during critical periods of development. This hypothesis is further strengthened by the absence of any recorded blood dyscrasias from the list of congenital anomalies in children who were exposed to atomic radiation during the first half of intrauterine life.[46] Anemia may have occurred, but not of sufficient severity, apparently, to have been noticeable.

THE SYNDROME OF NONHEMOLYTIC ANEMIA OF THE NEWBORN

Hemolytic and Nonhemolytic Types of Anemia of the Newborn.—Prior to the era of intensive investigation of erythroblastosis, reference was made to a clinical condition termed anemia of the newborn. This entity consisted of the sudden appearance of extreme pallor in an otherwise healthy infant within the first two weeks of life, resulting in a sheetlike whiteness. The anemia was profound and was not accompanied by erythroblastemia, enlargement of the spleen or liver, or of jaundice. Hemorrhage, hemolysis, infection, or birth injury were excluded as etiological factors. These infants recovered with or without transfusions and without sequelae. In similar cases classified under the same designation the course was complicated by varying degrees of jaundice, immature red cells in the peripheral blood, enlargement of the liver and spleen, and excessive extramedullary hematopoiesis, and the outlook was frequently unfavorable. Subsequent study revealed that siblings of the affected infant were observed to have well-defined hydrops or other evidences of icterus gravis. This pathological and clinical association provided strong support for the hypothesis that the three conditions were interrelated and that anemia of the newborn represented a milder form of the syndrome.[47] With the discovery of the Rh factor and the additional knowledge that erythroblastosis also resulted from incompatibility of the major blood groups, this relationship was confirmed and interest in anemia of the newborn as an entity waned.

In certain infants, however, anemia of moderate severity is noted at birth or within the first week of life which cannot be explained on the basis of established etiologies. In these instances, evidences of overt bleeding, hemolysis, and early or excessive jaundice are absent and the blood groups of mother and infant are compatible. Other pathogenetic mechanisms must be considered and pending their precise definition it was thought desirable to modify the older terminology and to designate this condition as the syndrome of nonhemolytic anemia of the newborn.

Clinical and Hematological Features of Nonhemolytic Anemia of the Newborn.—To this category have been assigned infants who at birth or within the first weeks of life reveal hemoglobin and red cell values that are strikingly lower than the average for a comparable age period. The red cells are otherwise normochromic and normocytic, occasionally macrocytic, and normoblasts are not increased in number beyond the normal. The bone marrow is anatomically normal with respect to the percentage of each of the cellular elements. These blood findings are encountered either quite unexpectedly in the course of routine examination, or because of moderate to marked pallor. The spleen and liver are not enlarged and icterus, at best,

TABLE IV. CASE 1, G. R., BORN JUNE 7, 1949

DATE 1949	HEMOGLOBIN GM. PER CENT	RED CELLS MILLIONS PER CU. MM.	ADDITIONAL DATA
6/8	14.2	4.10	Mother—O, Rh positive Infant—O, Rh positive Mild asphyxia at birth
6/13	11.8	3.27	
6/25	7.4	2.16	
6/28	6.4	2.14	Transfusion 75 c.c. blood
7/16	8.7	2.24	
7/18			Transfusion 80 c.c. blood
7/19			Transfusion 60 c.c. blood
7/28	8.8	3.33	
8/5	11.8	3.20	Bone marrow—18% nucleated red blood cells
10/12	11.1	4.31	4.5 reticulocytes

TABLE V. CASE 2, M. G., BORN OCT. 27, 1949

DATE	HEMOGLOBIN GM. PER CENT	RED CELLS MILLIONS PER CU. MM.	ADDITIONAL DATA
1949			
11/2	11.3	3.27	Mother—A, Rh positive Infant—A, Rh positive Bone marrow—14% nucleated red cells
11/3			0.7% reticulocytes Coombs negative
11/6	10.3		
11/8	9.5		Transfusion 70 c.c. blood
11/10	11.9	3.60	
12/9	12.0	3.21	
1950			
1/12	12.0	3.96	

is mild and occurs within the period of physiologic jaundice. These infants recover spontaneously, or with one or more small transfusions.

Several cases are briefly summarized in Tables IV, V, and VI to illustrate this hematologic entity. In no instance were abnormalities noted in relation to placental or aberrant umbilical blood vessels which could account for hemorrhage.

result of a third pregnancy and there had been no evidence of erythroblastosis in the two preceding children and no antibody production in the mother during gestation. The absence of isoimmunization was further confirmed by two negative Coombs tests in the infant on the first and second days of life. The involvement of the major blood groups was also eliminated when it was found that the mother was in group B and the infant in group O. The infant was clinically normal dur-

TABLE VI. CASE 3, D. C., BORN MARCH 18, 1952

DATE 1952	HEMOGLOBIN GM. PER CENT	RED CELLS MILLIONS PER CU. MM.	ADDITIONAL DATA
3/21			Mother—A, Rh positive Infant—O, Rh positive Coombs negative
3/22	8.7	2.39	0.3% reticulocytes Bone marrow—36% nucleated red cells Transfusion 64 c.c. blood
3/29	13.8	5.20	0.2% reticulocytes
4/14	13.0	4.42	
4/28	9.5	2.78	
5/1	11.0	3.80	Bone marrow—12% nucleated red blood cells 1% reticulocytes
5/2	10.2	3.50	Transfusion 75 c.c. blood
5/6	11.5		Bone marrow—36% nucleated red blood cells

TABLE VII. CASE 4, H. F., BORN NOV. 14, 1951

DATE 1951	HEMOGLOBIN GM. PER CENT	RED CELLS MILLIONS PER CU. MM.	ADDITIONAL DATA
11/14			Mother—B, Rh positive Infant—O, Rh positive Coombs negative
11/15	11.5	3.60	Coombs negative
11/16	12.0	4.07	
11/17	12.0	4.44	
11/20	12.0	4.42	

CASE 4.—This patient is considered separately because the difference in blood groups and Rh types in the mother and infant might on cursory observation lead to an erroneous diagnosis of mild erythroblastosis.

In this case (Table VII) the blood was examined as a routine measure because of the incompatibility of the Rh-blood groups. The infant was the

ing the period of hospital observation, and there was no peripheral normoblastic response nor enlargement of the liver or spleen and jaundice was absent. Anemia could not be attributed to incompatibility of blood groups or to other readily discernible causes.

Normal Blood Changes in the Newborn and the Pathogenesis of Neonatal

Nonhemolytic Anemia.—To explain the excessively low hemoglobin and red cell levels in this group of frequently asymptomatic newborn infants, it is necessary to examine the contemporary background for causative factors in and out of the hematopoietic system. Conceivably these lowered blood values already present at birth reflect a prematurely developed hypoplastic state since all evidences of hemolysis are absent. The marked anemia in these infants must be measured against the more moderate decline of prevailing blood values in the normal infant. The postnatal adjustment which is characterized by normal or slightly increased rate of blood destruction is accompanied by diminished or stationary hematopoietic activity. These changes are usually orderly and gradual and appear to be directed toward the establishment of a hematopoietic equilibrium designed to function at a lower level than exists at birth. While hemolysis accounts for the fall in hemoglobin and red cells, the continued decline represents a diminished rate of compensatory regeneration. The evidence for increased hemolysis in the newborn period is equivocal, at best, and recent studies[48, 49] indicate rather normal or, at best, slightly increased blood destruction. Physiologic anemia of the newborn may more properly be related to a depression of bone marrow activity during the early weeks, rather than to hyperhemolysis.[50, 51] The degree of anemia cannot be correlated quantitatively with the concentration of erythroid elements in the marrow. During the first week of life when the decline in hemoglobin and red cells in the peripheral blood is at a minimum, the bone marrow undergoes a marked drop in nucleated red cells.[52] The lowest levels are reached in the marrow between the end of the first and fourth weeks of life[53, 54] with a considerable increase in cells following this period. The hemoglobin and red cells continue to drop during the first two or three months regardless of the erythroid content, indicating a state of functional rather than anatomic hypoplasia and an inability to offset the fall in hemoglobin by increased blood formation. According to this concept, nonhemolytic anemia of the newborn represents a disturbance of normal regulatory mechanisms to produce an aggravation of the aregenerative phase, which may have been initiated during fetal life.

TABLE VIII. HEMATOLOGIC DATA ON BABY D, BORN DEC. 20, 1951, SHOWING SUSTAINED BLOOD LEVELS IN NEONATAL PERIOD*

DATE	HEMOGLOBIN GM. PER CENT	RED CELLS MILLIONS PER CU. MM.	RETICULOCYTES
1951			
12/29	18.0		
1952			
1/3	24.2	7.30	
1/4	20.6	7.40	
1/7	19.4	6.60	
1/8	22.8	7.50	
1/10	18.8	6.25	
1/12	20.4	6.70	
1/14	20.6	6.70	0.8
1/16	20.6	6.70	
1/18	19.4	6.90	0.5
1/22	18.8	6.00	0.5
1/24	17.4	5.95	0.7
1/26	18.1	6.40	0.2
1/28	17.4	5.85	0.2
1/30	18.1	5.90	0.7
2/2	18.1	6.20	0.4
2/4	15.8	5.15	0.1
2/11	15.4	5.05	0.1

*General condition at birth good; weight gain steady; hospital course uneventful; physical examination revealed no abnormalities. Chest x-ray on 1/9/52 normal; x-rays of skull and long bones on 1/17/52 normal; EKG on 1/17/52 normal; sternal marrow on 1/17/52 normal.

In exceptional instances, the disturbance of postnatal regulation of hematopoiesis may manifest itself in

the converse of nonhemolytic anemia of the newborn, resulting in a delay in the neonatal drop in blood values. This was observed in the full-term infant[55] recorded in Table VIII. This unusual stability of blood values in a healthy infant illustrates a delayed transition to the hypoplastic state, rather than to fluctuations of blood volume and hydration, persisting over such a prolonged period.

In addition to the hypothesis of aggravation of the aregenerative phase proposed in this paper, other explanations have been advanced for these excessively lowered blood values in the early neonatal period. Lehndorff[56] relates "transitory anemia of the newborn" to the elaboration of a marrow-inhibiting allergen resulting in anemia which may extend to the white cells to produce a granulocytopenia. This shocklike mechanism inherent in the newborn infant manifests itself usually at the end of the first week of life by producing sudden profound anemia, slight icterus, and spontaneous recovery within a short period. The tardy development of this hemolytic disorder as compared with the prompt postnatal appearance of the anemia previously described may conceivably separate the two conditions, although they may eventually prove to be related by a common pathogenesis.

The type of neonatal hypoplastic anemia that has been described requires further elucidation in the light of recent anatomical studies by Javert[57, 58] and Kline.[59, 60] They demonstrated microscopic defects or breaks in the villi, permitting leaks of fetal blood into the maternal circulation in both erythroblastosis and in normal pregnancy resulting in hematomas. Wiener[61] suggested that, whereas post-hemorrhagic shock and severe anemia in the infant complicated major bleedings such as occurred in abruptio placentae, placenta previa, and vasa previa, minor degrees of anemia unrelated to erythroblastosis could result from occult placental hemorrhage. In documenting this thesis, Wickster[62] reported cases of anemia in newborn infants, illustrating each category of bleeding from placental and umbilical blood vessels, with a fatal outcome in instances of extensive exsanguination. The role of concealed hemorrhage from the fetal surface of the placenta awaits microscopic studies to correlate the presence of anatomic defects and hematomas with the occurrence of anemia in the nonerythroblastotic newborn infant.

The cases that have been cited to illustrate this syndrome are still few in number, and its pathogenesis awaits more extensive experience. Undoubtedly, among the cases of anemia of the newborn described by Greenthal,[63] Pasachoff and Wilson,[64] Lehndorff,[56, 65] Cohen and Shapiro,[66] Abt,[67] and many others will be found instances of a similar type, but these could not be distinguished from erythroblastosis in the period when their reports were published. The category of nonhemolytic anemia of the newborn, therefore, has been revived to include those infants who show a rapid fall of red cells and hemoglobin within the first days of life, without jaundice and erythroblastemia. In these cases, the factors of incompatible blood groups, hemorrhage, hemolysis, and infection are not operative, and the outlook, based on a limited experience, is uniformly favorable. The designation as "nonhemolytic anemia of the new-

born'' emphasizes its differentiation from erythroblastosis.

TEMPORARY HYPOPLASTIC STATES

Acute Erythroblastopenia and the Aplastic Crisis.—Owren's[68] recent studies provided an alternate mechanism to that of hyperhemolysis to explain the abrupt drop in hemoglobin and red cells that characterizes the course of spherocytic anemia. He demonstrated that an aplastic, rather than a hemolytic, crisis should be suspected when sudden anemia is accompanied by the disappearance of reticulocytes, by increased pallor rather than jaundice, and often by varying degrees of leukopenia and thrombocytopenia. Instead of an increased hyperplasia, which marks a hemolytic crisis, the bone marrow in the aplastic crisis usually reveals the complete absence of erythropoiesis, the occasional presence of proerythroblasts, a shift to the left of the granulocytic series, and a decrease of megakaryocytes. To these significant features, Singer, Motulsky, and Wile[69] added an increase in plasma and reticulum cells in the marrow, and emphasized the disappearance of polychromatophilic red cells from the blood smear. From the study of a child with sickle cell anemia who developed an acute erythroblastopenia during the course of a virus infection, they evolved several important principles relating to its dynamics. They demonstrated that the severity of the anemia following sudden aplasia depends upon the presence or absence of a pre-existing hemolytic state on the one hand, and the inherent survival time of the red blood cells in a particular individual on the other. Normally, the red cell count reflects a balance between the rates at which erythrocytes are delivered from the marrow and their destruction in the circulation. The extent of anemia during an aplastic crisis can be correlated with the duration of red-cell inhibition and their normal survival rate in the blood stream. The degree of anemia would be less marked in the individual with a rate of destruction corresponding to the normal 120-day lifetime and exaggerated in the patient with spherocytic or sickle cell anemia whose defective red cells possess a shorter life span.

During the recovery phase, the marrow reverts to its hyperplastic stage with the reappearance of erythroblasts and normoblasts in various stages of maturity followed within a week by peripheral reticulocytosis. Thus a maturation arrest at the erythrogone or proerythroblast level short of a total depletion of erythropoietic tissue has been interpreted by Dameshek and Bloom[70] during the crisis of hereditary spherocytosis as an extreme degree of hypersplenism. The role of ''splenic inhibition'' in the pathogenesis of certain cases of an aplastic crisis remains conjectural and depends in large measure on the extent of residual erythropoiesis observed in the bone marrow. The designation of a bone marrow as being in the state of arrest, rather than of aplasia, stems from the degree of erythroblastopenia. The aplastic state is transitory and different concepts may result from examination of the bone marrow during successive stages of returning erythropoiesis.

Infection, regarded as a common etiological factor, may precipitate an aplastic crisis in patients with or without prior hemolytic anemia. Chernoff and Josephson[71] reported an acute

transitory erythroblastopenic crisis in a patient with infectious mononucleosis and pointed out the diagnostic difficulties in the absence of a hemolytic anemia. The only means of determining the cause of the slowly progressive drop in hemoglobin and red cells in this circumstance rests upon the recognition of diminished erythrocyte activity in the bone marrow. In this connection, Gasser[72] recently reported an acute but temporary disappearance of the normoblasts from the bone marrow in a group of children known to be allergic and induced by infection or a drug.

Table IX. Temporary Depression of Erythropoiesis in the Course of Erythroblastosis
Baby R. K., Born Sept. 27, 1951

Bone marrow aspirations	1951 10/11	10/24	11/1	11/8	11/23
Total nucleated cell count per cu. mm.	23,000	47,000	21,000	28,500	86,000
Megakaryocytes per cu. mm.	44	0	0	11	33
Myeloblasts	0	0.5	0	0	0
Myelocytes	12	2.25	9.5	4.0	10.5
Metamyelocytes	2	0	1.0	0	0
Polymorphonuclears: nonsegmented	8	6.5	4.0	7.5	11.0
segmented	9	20.0	8.0	2.0	2.5
Eosinophils	0	5.5	0	0	0
Lymphocytes	43	58.0	76.0	78.5	50.0
Nucleated red cells	26	7.5	1.5	8.0	26.0

	9/28	10/9	10/11	10/24	11/3	11/8	11/23
Hemoglobin Gm. %	17.5	6.5	10.1	10.9	8.0	11.0	11.9

Treatment: 7 blood transfusions from 9/28 to 11/4—total = 390 c.c.
Blood groups: Mother O, Rh negative
Infant O, Rh positive

Since Owren's report, the occurrence of the aplastic crisis in the hemolytic anemias has been abundantly confirmed. The development of sudden profound pallor rather than accentuation of an anemia should suggest an aplastic rather than a hemolytic crisis. Which type of crisis supervenes is unpredictable and will depend ultimately upon the precise elucidation of factors responsible for either phenomenon.

The initial examination in a child in whom spherocytic anemia is unsuspected may prompt a diagnosis of aplastic anemia when a depleted marrow is discovered. This uncertainty is brief, however, for the bone marrow becomes extremely reactive within a short time, and accelerated erythropoiesis and marked reticulocytosis which follows is associated with the reappearance of numerous spherocytes in the peripheral blood. Similar difficulties may be encountered in sickle cell anemia and in idiopathic acquired hemolytic anemia, until regeneration sets in and further tests establish the actual nature of each disease.

Erythropoietic Depression in the Course of Erythroblastosis.—With the exception of the aplastic crisis, the bone marrow in the hemolytic anemias almost uniformly reveals hyperplasia connoting increased blood formation to balance chronic blood destruction. In certain cases of erythroblastosis, a period of protracted anemia follows the first week or ten days of life, regardless of transfusion, and in these, examination may occasionally reveal a hypoplastic rather than a hyperplastic marrow.[73, 74] The inability of erythro-

blastotic infants to maintain normal blood levels can be explained as an exaggeration of the aregenerative condition which marks the neonatal period.

To appraise the significance of the hypoplastic marrow in refractory cases, it is important to take into account the substantial reduction in nucleated red cells occurring normally in infancy between the eleventh and seventeenth days and eight and thirty-third days, respectively.

To determine the extent to which erythropoiesis becomes depressed in the course of erythroblastosis, serial bone marrow aspirations were carried out in several infants during periods of persistent anemia. A decreased percent-

TABLE X. CHRONIC HYPOPLASTIC ANEMIA OF CHILDHOOD WITH RECOVERY
J. P., BORN JUNE 20, 1941

DATE	HEMOGLOBIN GM. %	RBC PER CU. MM.	WHITE BLOOD CELLS PER CU. MM.	POLYMORPHONUCLEAR NEUTROPHILS %	EOSINOPHILS	RETICULOCYTES %	ADDITIONAL DATA
1946							
11/15	10.0	2.99	7,900	53	7	0.5	12/5 Bone marrow: total nucleated cells 179,000 per cu. mm. Nucleated red cells 38%.
1947							Dec. 1946—Blood transfusion: total = 500 c.c.
7/2	10.7	3.45	6,700	42	4	1.0	7/11 Transfusion—500 c.c. Platelets 210,000 per cu. mm.
11/7	11.0	2.83	8,700	55	0	0.5	11/14 Transfusion—500 c.c.
1948							
2/27	11.0	3.72	5,500	50	1	2.5	3/19 Transfusion—250 c.c. Platelets 176,000 per cu. mm.
6/16	11.8	3.95	5,500	43	0	2.5	7/20 Transfusion—250 c.c.
9/23	12.0	3.84	10,600	58	1	2.5	11/9 Transfusion—300 c.c.
1949							
2/24	12.5	3.62	4,200	42	6	2.0	April—Tonsillectomy
7/15	13.0	4.10	9,000	45	3	0.5	
11/11	12.0	4.20	8,600	51	5	1.5	Platelets 210,000 per cu. mm.
1950							
7/17	12.0	4.10	5,400	40	8	1.0	Platelets 180,000 per cu. mm.

the neonatal period. Shapiro and Bassen[52] called attention to the marked drop in erythroid elements at the end of the first week of life. In these studies, Glazer, Limarzi, and Poncher[53] and Gairdner, Marks, and Roscoe[54] observed the lowest percentages in early age of nucleated red cells was observed in several cases regardless of whether treatment consisted of replacement or multiple transfusions. In two cases based on Rh incompatibility, the erythroid elements reached levels considerably below the normal. In one

infant previously described (patient K. H.)[22] these cells at the third, fourth, and seventh weeks numbered 7.0, 0, and 30 per cent, respectively. In the case outlined in Table IX, the low level of 1.5 per cent was reached at 5 weeks of age.

The temporary failure of erythropoiesis in these cases may be ascribed either to the exhausting effects of persistent hemolysis on bone marrow or to the inhibition of erythropoiesis induced by repeated transfusions or to the combined influence of both factors. It will be pointed out in a later section of this paper that multiple transfusions administered at frequent intervals to correct unstable blood levels may serve to further depress the inactive hematopoietic system such as characterizes the normal infant in the early months of life.

Table XI. Chronic Hypoplastic Anemia of Childhood With Recovery
J. L., Born July 18, 1940

Date	Hemoglobin gm. %	RBC per cu. mm.	White blood cells per cu. mm.	Polymorphonuclear neutrophils %	Eosinophils	Reticulocytes	Additional data
1952							
5/2	7.6	3.18	12,800	30	24		
6/9	6.8	3.43	11,200	52	6		
7/25	5.9	2.58	11,400	44	8		
7/28	6.9	3.60	19,900	42	14	2	Bone marrow: total nucleated cells 102,200 per cu. mm. Nucleated red cells 24%. 3 blood transfusions: total 750 c.c. Platelets 420,000 per cu. mm.
8/8	12.0	4.48	14,400	34	12		Cortisone 100 mg. daily for 6 weeks in Aug. and Sept., 1952, and intermittently for 2 months thereafter.
1953							
3/25	10.2	3.62	12,400	48	20		
4/2	12.0	4.74	21,200	49	10	4	Platelets 340,000 per cu. mm.

Chronic Hypoplastic Anemia With Recovery.—Occasionally prolonged ill-defined anemia is observed which in the absence of obvious etiological factors may be suspected to be an intermediate stage in the progress of idiopathic aplastic anemia. The normochromic and normocytic anemia is at variance with the bone marrow which is normal with respect to total cellularity and its various components including erythroid elements. The anemia is of moderate severity and resists treatment with iron and other hematinics and is corrected periodically by the administration of blood.

In the two cases to be cited (Tables X and XI), each child was known to be allergic, particularly toward the pollens, and to have suffered from severe upper respiratory infections. Recovery which ensued in both may have been spontaneous or was perhaps related in one (J. P.) to tonsillectomy and in the other (J. L.) to prolonged cortisone therapy. The resumption of normal blood levels coincided with an amelioration of allergic and respira-

tory symptoms, but not in their entire elimination.

The anemia associated with infection does not result from a failure to absorb iron[75] but to an impairment in the utilization of iron for hemoglobin synthesis.[76, 77] The allergic child is known to be subject to frequent respiratory infections and it is possible that one or both factors contribute to the pathogenesis of the anemia. The precise manner in which tonsillectomy in one patient and steroid therapy in the other were related to restoration of normal blood levels remains obscure. The fact that chronic hypoplastic anemia in childhood may terminate in recovery is significant.

APLASTIC ANEMIA

Diagnostic Features.—True aplastic anemia with an acellular bone marrow and the typical picture of profound anemia, leukopenia, neutropenia, and thrombocytopenia is a rare occurrence in infancy and childhood. Pierce[78] estimated that approximately forty cases have been reported in children. The marrow reveals progressive hypoplasia although scattered areas of normal composition may be noted in samples from different sites. The anemia develops insidiously and diagnosis before pancytopenia is fully visualized is often difficult to establish. Hemorrhage based on thrombocytopenia or a blood picture of chronic anemia may constitute the dominant features until the deficiencies of the other cellular elements appear. Acute lymphoblastic leukemia in the leukopenic stage may simulate aplastic anemia, but microscopic study of aspirated marrow usually reveals the precise nature of the illness. With an acellular marrow the additional recourse to the use of concentration, and volumetric bone marrow aspiration techniques as described by Sturgeon[79] has facilitated the differentiation between the two diseases. A contracted or absent myeloid-erythroid (nucleated cell) layer and normal or increased percentage of fat in aplastic anemia are contrasted with leukopenia in which the fatty layer is absent and the myeloid-erythroid layer is variable. Enlargement of the lymph nodes and spleen usually present in acute leukemia is absent in aplastic anemia.

Aplastic Anemia in Association With Chloramphenicol.—The search for a history of exposure to agents injurious to the hematopoietic system is usually unsuccessful and most cases of aplastic anemia are eventually classified as idiopathic. Recently, myelotoxic effects have been reported in connection with chloramphenicol, resulting in frequently irreversible aplastic anemia. This complication confirmed the predication of Smadel[80] who called attention to the potential toxicity for bone marrow of the nitrobenzene radical in the chloramphenicol molecule. The suggestion that children are especially susceptible to marrow damage with respect to this drug[81] prompts an analysis of the hematologic changes that may complicate its use. For the large number of drugs which may induce bone marrow damage, Osgood's[82] recent review may be consulted.

Lewis and his associates[83] segregated a total of fifty-five blood dyscrasias that could be related to the use of chloramphenicol as the sole therapeutic agent. Of these, forty-four were cases of aplastic anemia with a fatal termination in twenty-three. Accumulated evidence has emphasized that

this condition is likely to occur in susceptible individuals who have taken this drug over prolonged periods, or who have been exposed to it intermittently. It should be emphasized that the incidence of these untoward myelotoxic effects is extremely low in comparison with the large number of patients who have received this drug. Thus, Alexander,[84] commenting on the efficacy of chloramphenicol in meningitis, particularly of *Hemophilus influenzae* meningitis, states that she found no evidence of aplastic anemia in giving the drug for ten days in large doses.

As with other chemicals which suppress hematopoiesis, it is difficult to isolate the sensitive individual in whom treatment may be complicated by serious hematologic reactions. Since chloramphenicol has proved a highly effective antibiotic and the agent of choice in specific clinical conditions, it is important to control its administration by frequent hematologic studies. The inhibitory effect on the bone marrow varies so widely with each patient, that for ultimate safety, the peripheral blood should be followed almost daily, and with suspicious changes, the bone marrow should receive prompt scrutiny. With few exceptions, available reports have shown that once platelets are substantially reduced, the condition is irreversible, and when pancytopenia is complete, cases terminate fatally and with severe hemorrhage. Of value, therefore, are the reports that withdrawal of the drug at the stage of granulopenia and anemia resulted in reversibility with complete hematopoietic recovery.[83, 85] Occasionally, the early toxic effects are reflected in a drop in platelets.[86] Osgood[82] points out that in the drug-induced blood reactions, the normally shortened life span of platelets and granulocytes as compared with the prolonged survival of erythrocytes results in the earlier appearance of thrombocytopenia and granulocytopenia than of anemia. Judging from available reports, however, serious bleeding associated with the marked reduction of platelets is a later development than granulocytopenia and anemia in chloramphenicol toxicity. In the present state of knowledge, periodic blood studies are, therefore, essential in detecting the stages of granulocytopenia, anemia, and possibly reduction in platelets, with the hope of forestalling severe thrombocytopenia and progressive marrow aplasia.

In the bone marrow, signs of injury consist of a sudden shift to an immature level, the presence of promyelocytes and myelocytes, a marked reduction in the more mature elements, and an increase in stem cells and lymphocytes. Volini and his associates[87] demonstrated the close association of erythroid maturation arrest of the marrow at the normoblastic level with the development of anemia. Additional precautions are necessary in the case of unduly long or repeated administration in the known allergic individual. With the first signs of bone marrow suppression, the drug should be discontinued, and energetic treatment should be instituted.[82] This should include transfusions, other antibiotics, cortisone, and ACTH to tide the patient over the critical period, until spontaneous recovery occurs. It is obvious that for the type of acute sensitivity described by Cone and Abelson[88] in which aplastic anemia occurred in a child of 6 years, after only

two days of chloramphenicol dosage, no safeguards seem possible.

BLOOD TRANSFUSIONS IN THE HYPOPLASTIC-APLASTIC ANEMIC STATES

Suppressive Effects on Erythropoiesis.—It was suggested previously that multiple blood transfusions might account for the drop in total cellularity of the bone marrow in pure red-cell anemia and for the protracted anemia occasionally observed in erythroblastosis. In addition, the appraisal of a specific hypoplastic blood picture is occasionally obscured by previous infusions of blood. The failure to obtain a sustained elevation of blood levels in this group of anemias stems in the main from the intrinsic defect in red cell formation and to a lesser degree from the possibility of a delayed effect of the blood in retarding erythropoiesis. This retarding effect can be detected by serial examination of the blood smears of patients with chronic anemias, either hemolytic or hypoplastic, receiving periodic transfusions. The predominance of donor cells and the sparse appearance of the characteristic cells of a particular anemia for prolonged periods following the administration of blood suggest interference with erythropoiesis in the recipient.

The depressant effects of blood administration have been investigated for many years, but there has been a reawakening of interest in this subject in recent years. The prominence of the corrective effects of transfusion tends to overshadow secondary inhibiting effects. The evidence for the diminished bone marrow response has been largely based on artifical polycythemia produced in experimental animals and in man. Robertson[89] observed a decrease in the number of reticulated cells in the circulating blood and bone marrow of rabbits rendered plethoric by transfusion. In the era before specific therapy, he also noted that in pernicious anemia a feebly reacting bone marrow could be markedly depressed by the sudden introduction of a large volume of blood into the circulation and therefore suggested the advisability of small transfusions. Emlinger, Huff, and Oda,[90] reviewing previous studies revealing lessened erythropoiesis during the early weeks following transfusions, contributed confirmatory observations in animals with the use of tracer iron technique. Birkhill, Maloney, and Levenson[91] examined the effects of transfusion polycythemia upon bone marrow activity and erythrocyte survival in normal young adults. A temporary depression of erythropoiesis directly related to the quantity of red cells infused was indicated by a decrease of reticulocytes in peripheral blood, of erythroid cells in the marrow, and a progressive fall in the subject's own red-cell mass.

The relationship of oxygen tension to the control of erythropoiesis is also pertinent in an appraisal of long-term transfusion effects. A decline of red blood cell and reticulocyte values by the exposure to high concentrations of inspired oxygen was demonstrated by Boycott and Oakley[92] in animals, by Reinhard and his associates[93] in patients with sickle cell anemia, and by Tinsley and his associates[94] in normal and anemic individuals. These studies confirm the generally accepted principle that anoxemia serves as a stimulus for erythropoiesis, while high oxygen tensions act as a depressant. In applying the latter observations, Molli-

son[48] points out that in erythroblastosis the rapid lowering of the infant's own red cells following a large transfusion of Rh-negative cells may be attributed in part to the lessened stimulus to the marrow because of the increased availability of oxygen from the transfused cells. To what extent the observations that have been cited apply to the chronic anemias of infants and children, whether hemoglobin synthesis and erythrocytogenesis are influenced by similar mechanisms, and the possible role of factors other than oxygen tension on the responsiveness of bone marrow, are under current investigation and will be reported in a subsequent communication.

The possibility of aggravating or prolonging a hypoplastic state by inappropriate spacing of transfusions is conceivable from the empirical regimens employed in treatment. An analysis of the varied effects of blood administration on erythropoiesis, such as the optimum size of transfusions and their spacing, warrants special consideration in refractory anemias in which the infusion of blood constitutes the sole treatment. It should be emphasized that the hemoglobin level at which a transfusion is indicated in chronic anemia, nonhemolytic as well as hemolytic, cannot be arbitrarily fixed but varies with the associated clinical signs and symptoms manifested by the individual patient and promise of their relief.

SUMMARY

From the heterogeneous group of hypoplastic-aplastic anemias, several well-defined clinical and hematological entities and distinctive blood responses have been chosen for review. These are normochromic and normocytic syndromes differentiated from other blood dyscrasias by the absence of active blood formation and their resistance to all forms of antianemia treatment except transfusion.

These anemias have been placed into the three general categories of pure red-cell, hypoplastic, and aplastic anemias, in accordance with specific criteria.

In pure red-cell anemia the failure of the bone marrow is confined to erythropoiesis, without simultaneous depression of granulocytes or platelets or their precursors. These patients survive long periods, provided repeated transfusions are administered to maintain normal blood levels. An adequate appraisal of therapy is not yet available because of lack of experience with large numbers of cases. However, spontaneous remissions have been observed, as well as recovery with steroids and following splenectomy.

It was postulated that pure red-cell anemia and related hypoplastic anemias represent examples of congenital hematopoietic anomalies comparable to other somatic malformations originating from disturbances in embryonic and fetal life.

The syndrome of "nonhemolytic anemia of the newborn" was described to include those infants who show a rapid fall of red cells and hemoglobin within the first days of life, without jaundice and erythroblastemia. The factors of incompatibility of blood groups, hemorrhage, hemolysis, and infection are not operative and the outlook based on a limited experience has been favorable. The syndrome probably represents an exaggeration of the aregenerative phase of erythropoiesis which characterizes the newborn period. The designation as "nonhemo-

lytic anemia of the newborn'' emphasizes its differentiation from erythroblastosis and probably coincides with some of the cases of anemia of the newborn reported before the discovery of the Rh factor.

The mechanism of acute erythroblastopenia and the aplastic crisis was reviewed in connection with their occurrence in hemolytic states such as sickle cell and spherocytic anemias. Under these circumstances the initial examination without knowledge of a pre-existing hemolytic anemia suggests a diagnosis of aplastic anemia. The bone marrow soon becomes reactive and the underlying condition is manifest.

The temporary failure of erythropoiesis accounts for the observation of protracted anemia in occasional cases of erythroblastosis. This inability to maintain normal blood levels may depend upon an inactive bone marrow as evidenced by a decreased erythroid cellular content.

Two cases of chronic hypoplastic anemia were described which were suspected to be intermediate stages of aplastic anemia. In each instance the child was known to be allergic and susceptible to severe upper respiratory infections. The anemias resisted all hematinics except transfusion. Both children eventually recovered probably spontaneously although the effect of tonsillectomy in one and cortisone in the other could not be discounted.

True aplastic anemia with an acellular bone marrow and pancytopenia is a rare occurrence in infancy and childhood. While search for a myelotoxic agent is usually unsuccessful, chloramphenicol has occasionally been associated with toxic hematopoietic effects. Since this drug has proved the agent of choice in specific clinical conditions, it is important to control its administration by frequent hematologic studies. Precautionary measures including blood and bone marrow examination have been outlined to detect reversible anemia and granulocytopenia.

The possible suppressive effect of long-continued transfusions on erythropoiesis in any type of chronic anemia, nonhemolytic as well as hemolytic, may obscure the capacity for inherent blood formation and interfere with the appraisal of a specific blood picture. The optimum amount of blood to be administered and the interval between transfusions require serious consideration. Of major importance is to determine the actual need for transfusion, not in terms of a fixed hemoglobin value, but in relation to the clinical signs and symptoms manifested by the patient, with promise of their relief by this form of treatment.

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Psychologic Aspects of Pediatrics

THE RELATION OF CARDIAC DISEASE TO FEELINGS OF FEAR

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CRUICKSHANK[2] has stated that "fear and anxiety serve as motivating and inhibiting factors to healthy social, emotional, and academic adjustment and achievement." In recognition of the importance of fears in striving for healthy adjustment, much work has been done on their nature and etiology. For the most part, it has been difficult to establish causal relationships between fears and other factors. However, such relationships have been demonstrated in some cases as, for example, between children's fears and those of their parents.

Recently, Cruickshank[2] contributed evidence on another of these relationships. He found that children handicapped by a variety of physical disabilities, principally cardiac conditions, poliomyelitis, and cerebral palsy, perceived themselves as having more fears than nonhandicapped children and that the fears were directly related to their being handicapped. That which most significantly differentiated these children from matched nonhandicapped children were their fears of their handicaps.

A more recent study[5] has indirectly questioned the practice of studying the problems of handicapped children as a whole. It was found that cardiac children adjusted to members of their families differently from children handicapped by a number of other physical disabilities. One of the pertinent conclusions drawn from this study was that the "cardiac group was more similar to its control (nonhandicapped) group than the whole handicapped group was to its control group." It was possible to differentiate between a cardiac handicap and other handicaps, such as blindness or poliomyelitis, on three counts: a cardiac dysfunction (a) less severely inhibited the establishment of good intrafamily relationships, (b) was less externally evident, and (c) did not necessarily directly limit the behavior of the child. The present paper is a further investigation, in the area of fear and anxiety, of the similarities and differences between a group of cardiac children, a mixed handicapped group, and a group of physically normal children.

THE METHOD

The method used in the present study has been described in an earlier publication[1] and will be reviewed briefly. A Projective Sentence Completion Test was compiled by Cruickshank[1] to investigate various areas of adjustment, one of which was fear, the subject of the present paper. Following administration of the test to 264 handicapped children in six centers of the United States and to 400 nonhandi-

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capped adolescents, 264 of the latter group were matched with the handicapped children with respect to age and sex. Seventy-five of the handicapped children had a cardiac disability but the tests of four of these were not scored due to total illegibility of responses. The subjects of the present study were, therefore, the seventy-one cardiac children and their matched, nonhandicapped, controls.

Responses to the sentences were classified in terms of the feelings expressed in the completions. Two additional categories were included, (a) "omission," where no response was given, and (b) "unclassified," where the response could not be conveniently classified or was illegible. Utilizing judges, a high reliability was obtained for this procedure. The sum of the responses for each sentence was regarded as 100 per cent and the statistical treatment of the data consisted of the conversion of the frequencies in each category into percentages, the calculation of standard errors and critical ratios[3] and the determination of the associated probability values.[4]

RESULTS

For the purposes of clarity and brevity, data on the responses to two of the projective sentences have been brought together into one- or two-word categories expressing the essential feeling of the completion. Table I contains data on two sentences investigating fear situations, "I'm afraid of . . ." and "I wish I could stop being afraid of . . ."

From the first of these sentences, "I'm afraid of . . . ," it was hoped that a purely descriptive statement of feared situations would be obtained. Two categories of responses to this sentence especially distinguished between the cardiac children and the nonhandicapped children, (1) "interpersonal relations," and (2) "my handicap." Significantly more of the nonhandicapped children evidenced a fear of interpersonal relationships than cardiac children. This fear was also demonstrated in related areas such as "not being successful," "misbehaving," and "education," which are all related to social conformity and to all of which, a greater (though not significant) percentage of nonhandicapped than cardiac children responded. The one area in which more cardiac children than nonhandicapped children evidenced social anxiety was "family" and was probably related to the difficulty in adjustment with the mother experienced by the cardiac child and also his inability to participate in family activities.[5]

Probably the reason fewer cardiac children feared social contacts was that they had been excluded from such experiences by their handicaps. If this is true, then it would appear that the different responses of the cardiac children were directly attributable to their handicap. This follows from the fact that the other significant differences which were found were in the categories of "handicap" and "death." It is not too difficult to relate responses of "high places," "vehicles," "war," "accidents," and "hospital," more of which were given by cardiac children, to instances wherein injury and possible handicap could occur.

Cruickshank[2] stated that "the regressive type of adjustment characterizing the handicapped children is substantiated by the fact that the handicapped group gives larger percentages of those responses which we

would expect from younger children." According to data presented here such a statement does not seem warranted for cardiac children. It is true that more cardiac children than their controls gave responses indicating fear of "animals," "fire," and "high places." On the other hand, responses indicating fear of "darkness," "storms," should be so classified is one of individual choice. It would seem to the authors that "I am afraid of nothing," *is* a vague, immature response, expressing an infantile, undifferentiated feeling. If this is true, then Cruickshank's conclusion, based on his total handicapped group, does not seem applicable to the cardiac children in this study.

TABLE I. RESPONSES OF CARDIAC AND NONHANDICAPPED CHILDREN TO SENTENCES INVESTIGATING FEAR SITUATIONS

	UNCOMPLETED SENTENCES					
	I'M AFRAID OF . . .			I WISH I COULD STOP BEING AFRAID OF . . .		
RESPONSE	CONTROL GROUP % RESPONSE	NONHANDICAPPED GROUP % RESPONSE	P	CONTROL GROUP % RESPONSE	NONHANDICAPPED GROUP % RESPONSE	P
Interpersonal relations	5.0	18.0	.001	16.5	42.9	.001
My handicap	8.9	---	.005	4.1	---	.07
Death	3.8	---	.08	2.7	---	.17
High places	6.4	1.3	.08	5.5	1.3	.16
Storms	---	2.7	.17	2.7	1.3	.55
Not being successful	---	2.7	.17	---	---	---
Vehicles	2.5	---	.19	2.7	---	.17
War	2.5	---	.19	---	---	---
Accidents	2.5	---	.19	---	---	---
Misbehaving	2.5	6.9	.21	---	---	---
Education (school)	8.9	15.2	.23	9.7	6.9	.55
Animals	25.6	18.0	.25	18.0	16.6	.84
Hospitals	1.2	---	.27	2.7	---	.17
Family	6.4	2.7	.27	2.7	---	.17
Illness	---	1.3	.27	---	1.3	.27
Many things	---	1.3	.27	---	---	---
Nothing	5.1	8.3	.42	1.3	2.7	.55
Darkness	5.1	8.3	.42	6.9	9.7	.55
Fire	3.8	2.7	.72	2.7	---	.17
Unclassified	7.6	8.3	.88	6.9	4.1	.45
Omission	1.3	1.3	---	6.9	4.1	.45
Water	---	---	---	---	2.7	.17
My personality	---	---	---	4.1	4.1	---
Aggression	---	---	---	1.3	1.3	---
Vocation	---	---	---	1.3	---	.27

"many things," and "nothing" were found in more of the records of the nonhandicapped children. Also, on the "wish" sentence, more of the control children than the cardiac children evidenced fear of "water." The objection may be raised that completions of "nothing" and "many things" are not related to immaturity and, largely, the decision as to whether these responses The cardiac children do *not* give "larger percentages of those responses which we would expect from younger children."

An earlier finding[1] that more handicapped than nonhandicapped children are unable to evaluate their adjustment—as measured by responses of "omission" and "unclassified"—was not borne out in the case of cardiac chil-

dren. These two responses were the least significant of the differences in the responses to "I'm afraid of . . ."

In general, then, the cardiac children and their normal controls are more alike than different in their respective responses to this test. The outstanding differences were in the area of interpersonal relationships and in the reaction to the cardiac handicap. As previously mentioned, it is likely that differences in the latter response (cardiac handicap) were responsible for differences in the former response (interpersonal relations). Prohibited by cardiac dysfunction and/or his mother's perception of his handicap[5] from participating in social relationships, the cardiac child is not subject to the classical conflicts and turmoils occasioned by the adolescent's social adjustment and, consequently, he has less reason to fear them than the nonhandicapped child. In addition, those who react to the cardiac child may do so with deference and special attention. Thus, the cardiac child, having had less traumatic experience in interpersonal situations than the nonhandicapped child, has less reason than the latter to fear them.

The essential similarity between the cardiac and the nonhandicapped children in the area of feared situations is more evident in the responses to the sentence, "I wish I could stop being afraid of . . ." Only the category of "interpersonal relations" was significant at the 1 per cent level of confidence or better, with the control children producing more such responses. The only other response significant at the 10 per cent level or better was "my handicap." The nature of this incomplete sentence is different from the statement of "I'm afraid of . . ." The task of completing such a descriptive statement can be perceived as a most threatening one to the self.[2] As such, it is possible that prevalent fear situations may be suppressed. On the other hand, the sentence containing "I wish . . ." in a sense renders the threat one step removed from the self and, furthermore, by associating the fear with the fantasy of a wish, may make it less real for the individual. Therefore, it would seem that less guarded projection could be anticipated on the "wish" sentence. Furthermore, the wording of "stop being afraid of" would partially assure us that the completions refer to relatively long-term feelings which are high in the hierarchy of feared situations.

To return to the data, completions of "not being successful," "war," "accidents," "misbehaving," and "many things" were totally absent. Both groups showed percentage increases in the categories of "interpersonal relations," "darkness," and "omission," and both showed decreases in the completions of "animals," "family," "nothing," "fire," and "unclassified." Four new completions are to be noted, significant among which were "my personality" and "aggression." The former were similar to the category of "misbehaving" but sufficiently different (in terms of insight) to warrant separate categorization.

Again, the greatest shift occurred in the categories of "interpersonal relations" and "handicap." It is noteworthy that differences in only two categories were associated with significance levels of 10 per cent or better. In Cruickshank's study[2] of the group with a variety of handicaps, a much larger proportion of categories showed significant differences between the

handicapped and nonhandicapped groups (see Table II). For both sentences a higher percentage of categories was found significant at almost all levels between Cruickshank's total handicapped group and their controls than between the cardiac group and their controls.

One further uncompleted sentence, designed to investigate the reaction to fear, was included. This sentence was "My fears sometimes make me . . ." Equal percentages of the responses of both groups were found in the classifications of "nervous," "ashamed," "I have no fears," "sick," and "withdraw."

Only four categories were significant at the 10 per cent level or better. Responses of "afraid" were found in 25.0 per cent of the protocols of the nonhandicapped and in 7.0 per cent of the handicapped ($p = .002$); responses of "worry" constituted 5.6 per cent of the responses of the control group, and 0.0 per cent of the cardiac group ($p = .04$); and "unclassified" completions were found in 9.8 per cent of the records of the nonhandicapped and 1.4 per cent of the handicapped ($p = .02$). Only one response of the four significant ones was found more frequently in the protocols of the cardiac children. The completion, "do things" or "misbehave," occurred in 12.6 per cent of their records and in 1.4 per cent of those of the control group, the probability value being .006. It seems, therefore, that the normal children react to their fears by internalizing the feelings provoked by their fears while the cardiac children act out their fears. However, it is interesting that 5.6 per cent of the responses of the handicapped and 1.4 per cent of the responses of the nonhandicapped were "dream" ($p = .16$). Reference to the cardiac handicap was found in only 1.4 per cent of the cardiac children's responses ($p = .25$).

TABLE II. COMPARISON OF PER CENT OF TOTAL NUMBER OF CATEGORIES WHICH WERE SIGNIFICANTLY DIFFERENT FOR CARDIAC CHILDREN AND TOTAL HANDICAPPED GROUP

		UNCOMPLETED SENTENCES			
		I'M AFRAID OF . . .		I WISH I COULD STOP BEING AFRAID OF . . .	
GROUP		CARDIAC (%)	TOTAL HANDICAPPED (%)	CARDIAC (%)	TOTAL HANDICAPPED (%)
Per cent level of confidence at which difference was significant	1	9.5	13.3	5.0	12.9
	5	0.0	6.6	0.0	6.4
	10	9.5	6.6	5.0	19.3
Total per cent		19.0	26.6	10.0	38.7

CONCLUSIONS

1. A fear of their handicap significantly differentiated the cardiac group from their matched, physically normal controls.

2. A greater fear of interpersonal relations outstandingly characterized the nonhandicapped group. This difference is probably related to the handicap in that the cardiac children, having had less experience in social situations owing to their handicap, did not fear them as much as normal

children who had experienced more conflicts.

3. The data did not indicate that the adjustment of the cardiac child was regressive and immature.

4. Essential similarity, rather than difference, characterized the specific situations feared by both the handicapped and nonhandicapped groups.

5. As noted previously, in the adjustment to parents and family, the cardiac children were more similar to their control group than the total handicapped group was to its control group in the area of feared situations.

6. Grossly, the reaction of both groups to feelings of fear was one of withdrawal or internalization of the feelings. However, this was significantly more often the case in the nonhandicapped group than in the cardiac group. The evidence indicated that cardiac children may act out their feelings extratensively.

7. The cardiac children did not show the same degree of difficulty in evaluating their adjustment as do a group of children with miscellaneous handicaps.

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Comments on Current Literature

HISTOPLASMOSIS

KNOWLEDGE concerning the natural history of mycotic infection such as that due to the fungus, *Histoplasma capsulatum*, has been accumulating in recent years. The rather striking geographical distribution of this infection as demonstrated by histoplasmin sensitivity studies indicates that endemic foci exist in the Midwestern area of the United States. Missouri, southern Illinois, Indiana, Tennessee, Ohio and northern Arkansas comprise an area in which 70 to 90 per cent of the young adults have shown positive reactions to histoplasmin skin-testing material. Radiating from this central area of high incidence, the distribution of histoplasmosis infection in the human population extends to embrace parts of the neighboring states.

Extensive clinical studies carried out by Christie[1] and others[2] have emphasized the wide clinical spectrum of this disease from subclinical, inapparent, to benign apparent infection, to fatal illness. The occurrence of a large number of unrecognized infections accounts very likely for the high incidence of histoplasmin skin sensitivity in the endemic areas. Of particular importance clinically is the association of *H. capsulatum* with pulmonary involvement characterized by the presence of numerous discrete pulmonary infiltrations which on roentgenographic examination may simulate miliary tuberculosis.

In the June, 1953, issue of *The American Journal of Public Health*, Grayston and Furcolow[3] contribute significantly to the subject of histoplasmosis by presenting a summary of their extensive epidemiologic studies. These authors review their experience with thirteen epidemics of histoplasmosis in each of which it was possible to demonstrate a common source of exposure. The epidemics investigated included two in Missouri, two in Kansas, and one each in New York State, Illinois, Minnesota, Wisconsin, North Dakota, Iowa, Ohio, Arkansas, and Oklahoma. It is interesting that only three of these epidemics occurred in the area of greatest endemicity. Some of them were in areas of low histoplasmin sensitivity. On the basis of information concerning common exposure in eleven of the epidemics, the authors concluded that the incubation period averages from one to two weeks. In no instance was there evidence of secondary cases due to contacts with members of the family or with associates, without exposure to the common source of *H. capsulatum*.

Investigators have been remarkably successful in isolating the fungus from areas where a common source of infection seemed to be present. For example, *H. capsulatum* was isolated readily from soil samples collected in a storm cellar associated epidemiologically with an outbreak of unusual pulmonary disease among thirty-five soldiers at Camp Gruber, Oklahoma, in 1944. These men had occupied the storm cellar during field maneuvers, and all persons who were actually inside the cellar showed definite pulmonary disease, some severely affected, some less so. In connection with another study, Histoplasma was cultured from soil samples collected on a farm just outside Kansas City, Missouri. This location was approximately the original site of a chicken coop which had been torn down in July, 1947, by two grandparents and four

of their grandchildren. The four children and the grandmother became ill following this activity. In three of the children who were severely ill, roentgenographic studies revealed numerous miliary lesions. In all six of the individuals taking part in this cleanup project, grandmother, grandfather, and four grandchildren, histoplasmin skin-testing material gave positive reactions. Five of the six individuals experienced clinical manifestations of greater or lesser degree.

In the outbreak in Arkansas, twenty-five men and boys were ill with fever and pulmonary manifestations about ten days after digging out an old filled-in cave. Soil samples collected inside the cave yielded *H. capsulatum*. In Illinois in April, 1951, two 9-year-old boys experienced almost simultaneously a febrile illness associated with numerous disseminated infiltrations in the lungs. Both boys had climbed down into a hollow tree trunk, and had been imprisoned there for a period of about two hours. The boys had to be extricated by means of a ladder. Specimens of soil and fine debris taken from inside the trunk, and from the surrounding area yielded *H. capsulatum* on two occasions.

In other investigated epidemics the organism has been recovered from such sources as sawdust in an abandoned silo, a finely divided wood and soil mixture taken from a woodpile in Iowa, dirt removed from the basement of a church adjoining a school building which had been the source point of a rather extensive epidemic of histoplasmosis some months previously.

Usually outbreaks of the disease are associated with exposure to dust which in some cases was known to be contaminated with excreta from pigeons, bats, or chickens. In two instances workmen were severely ill with characteristic clinical findings who had been engaged in demolishing school buildings, the attics of which had been inhabited by bats or pigeons. These observations support the concept that the fungus, *H. capsulatum*, may be widely distributed in nature and that the most common form of clinical histoplasmosis is a pulmonary infection associated with the inhalation of contaminated dust materials.

As a result of their epidemiologic studies, Grayston and Furcolow state that the "recurring story" is one of "exposure to dust created by agitation of material proved to contain Histoplasma spores resulting after one to three weeks in illness associated with numerous discrete pulmonary infiltrations." While in the specimens collected for study close association with animal or bird excreta was often noted, there was no definite indication that the infection exists in animals or birds as reservoirs, but rather that the agent of histoplasmosis persists in the soil, and that the growth of the organism in soil is probably enhanced by high humidity. When material containing the fungus spores dries and is disseminated by whatever means, and when dusty, spore-bearing materials are agitated, the agent becomes air borne and clinical cases occur, chiefly in the pulmonary form of the disease.

In the entire group of cases discussed by these authors there were only two instances of generalized infection, both in older men. The one fatality in the group occurred in an infant 5 months of age. There is considerable evidence to suggest that inapparent, subclinical cases of histoplasmosis occur. Further evidence, some indirect, indicates that infection with *H. capsulatum* does provide resistance to reinfection, and that histoplasmin sensitivity in an individual probably indicates some measure of immunity. This suggestion seems to be borne out by various observations that epidemic outbreaks occur rarely in areas where high histoplasmin sensitivity has been demonstrated among the young adult population.

Widespread distribution of this fungus in nature could account for the unusual endemic and epidemic features of histoplasmosis. The striking demonstration, by recovery, of the presence of *H. capsulatum* at a common source in thirteen epidemics of

histoplasmosis, suggests that this mycotic agent can persist in infected soil, particularly in moist areas, for incredibly long periods. Under special circumstances human beings are exposed to infected material, usually in the form of dust, and it is likely that the common portal of entry in the human subject is the lungs by inhalation of infected material. The wisdom of avoiding exposure to excessive quantities of dust should be emphasized, and protection must be provided for persons who are required to carry on activities under circumstances in which such exposure is unavoidable.

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News and Notes

Dr. Julius B. Richmond, of the Department of Pediatrics of the University of Illinois, has been appointed Professor and Chairman of the Department of Pediatrics with the State University of New York Medical School at Syracuse. Dr. Richmond will serve on a full-time basis.

The Seventh Annual Meeting of the **American Academy for Cerebral Palsy** will be held on Oct. 30 and 31, 1953, in Ft. Worth, Texas, at the Western Hills Hotel. The scientific sessions are open to members of the medical or allied professions. Guests shall be required to pay a registration fee.

Book Reviews

The Surgery of Infancy and Childhood. Robert E. Gross, M.D., Philadelphia, 1953, W. B. Saunders Company.

Here, indeed, is a book which fills a great gap in medical literature. It not only deals with the surgical problems which the family physician, pediatrician, and surgeon meet in routine practice, but also covers unusual surgical conditions of infancy and childhood. The most important features of congenital deformities of the newborn infant amenable to surgical correction are covered in the text and by illustrations.

It is possible to stress only a few of the outstanding features of this most timely book. The text is clear, well written, to the point, practical, and notably free of filler. The illustrations are appropriate and well reproduced. An occasional illustration adds the zest of human interest.

It is a book which should be required reading, word for word, by every general surgeon. It should be at every pediatrician's side as a guide to the type of surgery which will yield the best results in children, especially those with congenital deformities. In fact, every doctor who in any way deals with the surgical problems of children will profit from reading this book.

It is a pleasure to review this book not only for the knowledge gained, but also because there need be no mental reservations in the laudatory statements. It is the sort of book about which one interested in this specialty would say, "I wish I had written that book."

WILLIS J. POTTS.

Bright Children. A Guide for Parents. Norma E. Cutts, Ph.D., and Nicholas Moseley, Ph.D., New York, 1953, G. P. Putnam's Sons. Price $3.50.

This book is designed as a guide for the parents of bright children. In a chapter on how to recognize the bright child, the authors emphasize the importance of developmental and clinical characteristics as well as psychologic tests. Most of the book is devoted to management. Discipline, school placement, choice of school, school difficulties, home supplements, and choice of a vocation are discussed.

The material is presented in a clear, concise, straightforward manner. The authors base their advice on their own experience and on an extensive survey of available literature. A bibliography is included. The book serves well the purpose for which it is intended.

H. B.

Child Development. William E. Martin and Celia Burns Stender, 1953, Harcourt, Brace and Company. Price $6.50.

This book deals, as the subtitle states, with the process of growing up in society. There are four subdivisions to the book: the child; society and culture; socialization; and socializing agents. The section on the child gives a well-rounded picture of individual development and the remainder of the book is devoted to a consideration of the child as he reacts to his social environment. Included here are all the social forces that influence a

child's development. The authors believe that the sum total of a child's personality is influenced at least as much by socializing forces as by his own innate potentialities. They see child development as not just an orderly sequence of events, but as a process which is conditioned by the sum total of the social environment in which it takes place; parents, teachers, peers, church, community, books, radio, television, and many other forces are all important in this socialization. This book draws on the sciences of sociology, anthropology, and psychology to develop its thesis. Its greatest interest should be to students of education. It does not answer the question of how a child should be educated but attempts to provide information which should assist in such decisions.

H. B.

The Book of Health. Compiled and Edited by R. L. Clark, Jr., M.D., and R. W. Cumley, Ph.D., New York, 1953, Elsevier Press Inc., 770 pages plus index. Price $10.00.

This amazing book on health information for lay readers may well be described as medicine gone Hollywood. It is purported to tell "what 242 doctors believe you and your family should know about medicine." Listed in its production are the names of the editors, an advisory board of twelve, writers, copy chief, production editor, art director, research librarian, artists, photographers, and even ten assistants, just as in a Hollywood film. And then in addition an "editorial board" of 242 doctors containing the names of the great, the near great, and some who have a long way to go to be designated as authorities. Let us make clear that they did not write the script for the various sections of the book, but are listed as having edited specific pages. Some must have done the editing in their sleep.

It is garishly illustrated. Of the 1,400 illustrations, many have been included whose choice must have been based on a promotion value rather than their value in furnishing lay readers with information of importance or use, which the average practitioner will "believe you or your family should know about medicine," for example, a double page of eight photographs showing the detailed surgical technique of a circumcision, or another full page of four photographs of the legs of patients with varicose veins. Another striking example in this category are eight photographs in color showing the surgical details of corneal transplantation. What possible reason or justification there is in presenting such illustrations in a "book of health" for the laity is difficult to figure out. Some of the illustrations even have a pornographic tinge, when published for lay readers, such as two and one-third pages presenting fourteen photographs of the development of the female breast at the ages 8 to 14 years, and a cut of a female with lines drawn to indicate where additional nipples may appear. Of the twenty color plates, some are totally without point as well as atrocious artistically. Of more interest are numbers of small cuts, scattered in appropriate places through the book, of physicians who have contributed to medical knowledge. Thus in the section on childhood we find Bordet, Wm. H. Park, Sydenham, and Bela Schick. For Schick the statement is made, "He founded the American Academy of Pediatrics." He was one of many "founder members" and would be the last to desire this inaccuracy recorded for posterity. Another inaccuracy we ran across in this group was the designation of Casmir Funk as an "American" biochemist. His classic monograph on the vitamins was published in German about 1910.

Turning to the written part of the script. As this is a review for a pediatric journal, we are concerned with the scope and accuracy of the text relating to pediatrics. This is chiefly found in Chapter 2, "the child." It starts with a discussion of the premature, and the definition of a premature is given as "any infant born less than 37 weeks after conception." No mention is made of the definition in common usage of an infant weighing less than 2,500 grams at birth, which is used by workers in this field and adopted by such organizations as the Children's Bureau and the American Academy of Pediatrics. It goes along to state that by the time the premature "is two or three years old he begins to 'catch up'" with full-term babies, and that "by the time he is four to six years old his de-

velopment often equals that of other children in his age group.'' Premature infants usually *begin* to ''catch up'' much earlier and *often* there are no traces left by eighteen months. Under the discussion of ''how the child grows'' the statement is made that ''Most American babies weigh from six to nine pounds at birth.'' Rather boastful. Under the heading ''rashes,'' ''a final rinsing in a saturated solution of boric acid'' is recommended for the diapers for babies with a diaper rash. Rather shocking bad advice to be found in a book on health. Our teaching in physiology was something different from ''The organs of digestion are not completely mature until the child reaches sexual maturity (*puberty*).'' Incidentally, it was news to the reviewer that the child reaches sexual maturity at puberty—perhaps the ovaries which are about 30 per cent of their ultimate weight at the time of the menarche develop more rapidly in Hollywood. The parts of this chapter that have to do with developmental levels, behavior problems, and childhood diseases are better. Turning to material in other sections of the book which deal with pediatric conditions we noted some further examples of inaccurate or careless statement. Thus in the discussion of polio the statement is made that in the 1951-1952 experimental studies of gamma globulin prophylaxis ''almost three times as many children who had not received gamma globulin had the disease as children who did receive the material.'' Those in charge of the study were most careful to base any claim as to the value of gamma globulin on a reduced incidence of paralytic cases. In another section on medical history, in a discussion of twentieth century advances in pediatrics stress is placed on the introduction of hyaluronidase in 1949, completely ignoring many far more important advances.

Whether the rest of the book contains as many careless and inaccurate statements as the pediatric material we are not qualified to state. Unusual length has been given to this review as it is apparent from the make-up of the book that a vigorous sales promotion will be made to the laity, as, for example, review copies being sent out in July although the publication date is September 23. Certainly it is a book we will recommend parents not to buy.

B. S. V.

ABC für Zuckerkranke. Prof. Dr. F. Bertram, ed. 5, Stuttgart, 1953, Georg Thieme, 72 pages. Price DM 3.60.

This is the fifth edition of a small book for the diabetic. It is excellent for the patient who reads German.

Les Antibiotiques et les Maladies de l'Enfance. Centre International de l'Enfance, London, 1953, Lange, Maxwell & Springer, Ltd., 298 pages. Price £3.3.0.

This is an excellently printed book containing the papers and discussions of a seminar held in Paris in September, 1952, organized by the International Children's Center at Paris, and held under the chairmanship of Sir Alexander Fleming. Over 100 participated from sixteen countries. In all, sixty-two papers were presented. The discussions were divided into three main groups. The first seventeen take up the action or use of antibiotics in the infections, as meningitis due to various organisms. Eighteen papers discuss the treatment of the various forms of tuberculosis in childhood, and six, the laboratory studies of resistance to the antibiotics. The remaining eleven papers consider other phases as absorption, mode of action, and synergism.

In all it is an interesting compilation of world thought and experience as of a year ago. With few exceptions the papers and discussions are in French. Only about ten are in English of which three were presented by Dr. Hattie Alexander, who was the only American taking an active part. Unfortunately, for some reason the summaries of the French papers have not been translated into English and other languages, as is customarily done in the reports of international conferences, which greatly detracts from the value of the book for many interested in the field. There are a number of very interesting papers for those who can read French without too frequent reference to a dictionary.

Editor's Column

GIFTS—WITH STRINGS ATTACHED

A REPREHENSIBLE practice is being reported by responsible physicians that unless checked can but lead to a serious rift in the present cordial relationship between physicians and certain commercial houses. Of more moment, if the situation is not corrected, it could seriously undermine the public's confidence in the integrity of the medical profession.

A few corporations are alleged to be making "philanthropic" grants to hospitals conditioned upon the use of their product. A well-known pediatrician writes that one large maternity hospital received as a "gift" an expensive apparatus for resuscitating the newborn infant and immediately thereafter the brand of milk that had been used satisfactorily for fourteen years was replaced by the donor's brand. Another hospital is said to have been given funds from the same source for the construction of an addition to the hospital contingent upon their using the donor's product. Still another institution was given three incubators and a contribution to the expansion of their formula room—all with the proviso that a specific brand of milk be used. A hospital group is reported to have been on the verge of accepting a substantial research grant from another company with the understanding that a particular preparation would be used, until a member of the pediatric staff heard about it and spelled out in plain English what was being proposed. The happy aftermath of this incident is stated to have been an apology from the company and the giving of the grant with no conditions attached.

Apparently the device by which this bribery has been accomplished by one corporation is through a charitable, and presumably tax-free, foun dation or trust. The trust or foundation makes the actual gift—but with the expressed or implied provision that a specific product be favored thereafter.

The pediatrician finds himself in a very unusual position with regard to the commercial houses whose products he prescribes. He is a middleman, but one who receives no personal gain as a result of the transaction. In his daily life the pediatrician is thrown in close personal contact with the representatives of many companies and he knows from these contacts that 99.9 per cent of these houses and their "detail men" are beyond reproach with a high sense of the ethics of their position. However, these corporations are engaged in a highly competitive business and must operate so as to show a reasonable profit. If necessary, they will be forced to fight fire with fire—with the chief loser being the reputation of the medical profession.

The cure for this one evil is very simple and many universities have already applied it—no conditional gift, expressed or implied, should be accepted by a physician, group of physicians, hospital, or medical school. This does not prevent a continuation of the present friendly practices of

ethical commercial houses in their open and aboveboard attempts to win the good will of doctors, individually or collectively.

Discussion of this problem with representatives of the milk industry reveals the fact that we as pediatricians have helped to create the very situation that has resulted in the present dilemma and we, therefore, must share some of the responsibility. It would behoove us to investigate conditions in our own institutions and to correct them in so far as we are able.

Providing food and accessory substances for our infant population is big business. With nearly 4,000,000 new babies last year this business is nearly twice as big as it was fifteen years ago. The regrettable loss of interest in breast feeding has of itself added to the demand for substitute foods. When we realize that in many states over 96 per cent of all births now take place in hospitals and recall that most infants continue to receive at home the type of formula started in the hospital then we understand industry's vital interest in having their products used in the hospital nursery.

Those in the milk business state, and we must admit it generally true, that in practically every hospital in the land there is one key individual who, one way or another, determines what type of formula shall be offered in that particular nursery. Every detail man knows who this person is in his local community and it is small wonder that every known approach will be utilized to gain favorable consideration for his product.

The provision of standard stock formulas for the feeding of all infants in the nurseries has come to be an almost universal hospital policy. The reason this practice has become established is largely one of economics plus the general shortage of trained nurses and auxiliary personnel. It would be practically impossible for a hospital today to provide an individual custom-made formula for each infant. In general, the standardized formula plan has worked out well from the point of view of the infant's welfare, the nursing and hospital administrations. Yet it is this stock formula, spokesmen for the milk industry claim, that is the chief cause for the type of malpractice being discussed. To have the one large maternity hospital, referred to earlier, use the same brand of evaporated milk for fourteen years, to the exclusion of equally good competing brands, means that approximately 50,000 babies have been sent home on this brand of milk with the prestige of the hospital's implied endorsement. One can understand why the evaporated milk producers, who are on the outside looking in, would be envious and consider such a monopoly unfair competition.

One large maternity hospital has taken steps to equalize this situation by ordering their purchasing department to rotate the orders for evaporated milk among the recognized brands represented in the area. However, it is pointed out that while this plan is a step in the right direction, it is not enough—the producers of fresh milk and of prepared formulas are not being recognized. A company representative holds that it is important for medical students and house officers to gain some experience in using the various types of foods that

they may wish to prescribe later in their practice.

It is difficult to see how everyone can be satisfied but we might try to remove the major inequities. Perhaps our hospitals might offer a choice of the three major types of formula —whole milk, evaporated milk, and prepared formulas. In each instance the purchasing department should be instructed to rotate orders among the recognized competitors. We are assured that such a system would automatically end one type of conditioned gift.

S. H. C.

SURGERY IN A CHILDREN'S HOSPITAL

IN READING the new *Surgery of Infancy and Childhood* by Gross, which is reviewed elsewhere in this issue by a surgeon, the editor was struck by the statement that in the opinion of the author the best results in pediatric surgery are obtained when surgery is an independent unit, and the entire preoperative and postoperative care is the responsibility of the surgical staff. This is the plan of organization started at the Boston Children's Hospital in 1927 by Dr. William Ladd and under which Dr. Gross has worked. The best evidence to support this viewpoint is found in this text. Some of the results in Boston are striking; for example, the results of surgery in the premature infant, and the steady reduction of the operative mortality rate for pyloric stenosis in a series of 1,787 cases from 1932 to 1951 as shown in Table 8 of the text. There are relatively few children's hospitals in the country with a similar organization, and with a surgical staff devoting their time exclusively to surgery in children. As one reads the introductory chapters on preoperative and postoperative care one is impressed by the breadth of knowledge of what is generally considered "pediatries" held by Dr. Gross, in addition to the purely surgical techniques.

On first thought it seems logical that this is the plan of organization our children's hospitals should attempt to obtain. After mulling the idea over for some time doubt began to enter in, and we began to question if it is the best plan for the development of surgical techniques applicable to conditions in childhood requiring surgery in their correction or treatment, particularly the best plan of organization for the care of the surgical patient for most children's hospitals.

In the first place Gross' text covers only a limited section or part of pediatric surgery. Of the sixty-six chapters in the book dealing with specific conditions, thirty-eight are concerned with the digestive system and intra-abdominal organs, nine with the genitourinary system, and six with cardiac surgery, leaving only a few for miscellaneous conditions. The surgical material at this hospital is enormous with 2,447 operations in the field of "general" surgery in 1950. However, we note that there were 407 neurosurgical operations in a special department of which Dr. Ingraham is in charge, 494 orthopedic operations, 1,877 otolaryngologic, 111 dental, and 64 ophthalmologic. The sum of these totals more than the operations in the

field of general surgery. No figures, moreover, are given for plastic surgery which constitutes no small part of the infant surgery in many hospitals for children. One wonders if all of the surgeons in these various fields have the same broad knowledge of anesthesia, antibiotic therapy, and fluid therapy as Dr. Gross and his staff in "general" surgery.

There is a great deal to be said, when pediatric surgery is looked upon as a whole, for the type of organization found in most children's medical centers where the pediatric staff is in constant touch with the surgical patients beyond the point of diagnosis. Relatively few children's services have the amount of material available which will enable a surgeon to confine himself to surgery in children. Nevertheless the surgical services in many of these hospitals have added much to the development of surgery in infancy and childhood. To cite some of the developments in a hospital where the other plan of organization is followed. It is the plan generally followed and this one is cited simply because the writer has personally watched it over a period of forty years. A number of the surgical staff have made significant contributions to the surgery of childhood, although none has confined his work to children. Vilray Blair, for example, has done much to advance plastic surgery in the newborn infant. Evarts Graham's pioneer work in thoracic surgery, like the work of Blair, received worldwide recognition. Ernest Sachs in neurosurgery and Caulk and Rose in genitourinary surgery have made definite contributions in their particular fields to the surgery of childhood. The same holds true for many surgeons in other institutions who do not confine their work to children. Blalock's work in cardiac surgery is an example that will flash through everyone's mind.

The question raised by Gross, and concerning which there can be honest differences of opinion, is whether pediatric surgery should be a special field, or whether surgery is best carried out by surgeons particularly qualified in a special field of surgery with the active cooperation and participation in the care of the patient by the pediatric staff. With due respect to the opinion of Dr. Gross, and with full appreciation of the splendid work and the important contributions to the development of the surgery of infancy and childhood made by the surgical staff of the Boston Children's Hospital, we believe that for the large majority of children's hospitals and services the plan of organization now in use at most institutions is probably better.